UNIVERSIDADE FEDERAL DE SERGIPE

PRÓ-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA NUTRIÇÃO

NAYARA BISPO MACEDO

PIMENTA ROSA (*Schinus terebinthifolius* Raddi): COMPOSTOS PRESENTES NOS FRUTOS E SUAS ATIVIDADES ANTIOXIDANTE E ANTI-INFLAMATÓRIA

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Nutrição como requisito parcial para obtenção do título de Mestre em Ciências da Nutrição.

Orientador: Profª. Drª. Ana Mara de Oliveira e Silva

SÃO CRISTÓVÃO/SE

2018

FICHA CATALOGRÁFICA ELABORADA PELA BIBLIOTECA CENTRAL

UNIVERSIDADE FEDERAL DE SERGIPE

Macedo, Nayara Bispo

M141p Pimenta Rosa (*Schinus terebinthifolius Raddi*) compostos presentes nos frutos e suas atividades antioxidante e anti-inflamatória / Nayara Bispo Macedo ; orientadora Ana Mara de Oliveira e Silva. – São Cristovão, 2018.

122 f. : il.

Dissertação (mestrado em Ciência da Nutrição) – Universidade Federal de Sergipe, 2018.

1. Nutrição. 2. Pimenta. 3. Antioxidantes. 4. Inflamação. I. Silva, Ana Mara de Oliveira e, orient. II. Título.

CDU 612.39:633.843

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Dissertação de mestrado aprovada no Programa de Pós-Graduação em Ciências da Nutrição em 10 de outubro de 2018.

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SÃO CRISTÓVÃO/SE

2018

AGRADECIMENTOS

À Deus, por estar sempre presente na minha vida.

À minha mãe e irmãs, pelo suporte e apoio em todas as minhas decisões.

À minha família, em especial meus sobrinhos, avós, tios e primos, pelo apoio e torcida constantes.

Ao meu noivo, João Ricardo, pelo amor, apoio e incentivo em todos os aspectos da minha vida.

À minha orientadora Ana Mara, pelo direcionamento, por compartilhar seu conhecimento e por ser, acima de tudo, um ser humano muito especial.

Aos professores Jullyana de Souza Siqueira Quintans, Marcelo Cavalcante Duarte, Enilton Aparecido Camargo, Arie Fitzgerald Blank, Adriano Antunes de Souza Araújo pela parceria de grande valia para realização deste trabalho.

Às parcerias de outros laboratórios, Juliana Oliveira de Melo e Bruno dos Santos Lima, que ajudaram na realização das análises, em especial Alan Santos Oliveira, pela paciência e solicitude.

Aos colegas do laboratório de Bromatologia da UFS, Andreza, Erivan, Raquel, Anne, Isadora e Suzane, por toda ajuda na execução deste trabalho e pelos momentos de descontração.

Às colegas da turma do mestrado Bruna, Laís, Layanne e Thiale – as Bioativas, pelo companheirismo e amizade ao longo dessa jornada.

Às professoras do Programa de Pós-Graduação em Ciências da Nutrição da UFS, pelos ensinamentos fundamentais na formação acadêmica.

À banca de qualificação e defesa, professores Elma Wartha, Marcelo Duarte, Thallita Rabelo e Luana Heimfarth pela participação e pelas valiosas contribuições.

À CAPES pela concessão da bolsa.

A todos que direta ou indiretamente ajudaram ou transmitiram energias para a realização deste projeto, muito obrigada!

“Eis uma mãe orgulhosa
E cheia de gratidão
Ver Nayara nessa batalha
Firme e com pés no chão
Sei o quanto ela estuda
Com renúncias e abnegação
Agradeço infinitamente
Só tem Amor no meu coração.
É uma mesa de mulheres
Com muito emponderamento
12 discípulas ensinando
Com muito comprometimento
Somos o futuro do mundo
Mesmo com esse momento
Sou mãe de três grandes mulheres
Eis meu maior contentamento
A todos vocês aqui presentes
Meu profundo agradecimento!”

(Nadja Tavares Bispo)

RESUMO

Schinus terebinthifolius Raddi, popularmente conhecida como pimenta brasileira ou pimenta rosa, é comumente utilizada para fins medicinais e apresenta importante potencial econômico e gastronômico para a população brasileira, além de ser amplamente utilizada na culinária francesa, no Peru e Chile. Estudos recentes demonstram que o consumo de especiarias pode contribuir para a redução do risco de doenças crônicas, e esta proteção está associada principalmente às propriedades antioxidante e anti-inflamatória. Desse modo, objetivou-se identificar e quantificar os compostos presentes no fruto da *S. terebinthifolius*, nos extratos e óleo essencial, além de avaliar a capacidade antioxidante e anti-inflamatória. Foi realizada a determinação do teor de compostos fenólicos e flavonoides totais nos extratos aquoso e etanólico e de terpenos no óleo essencial, por meio de análises colorimétricas e cromatográficas, bem como a avaliação da atividade antioxidante por diferentes métodos *in vitro* incluindo métodos baseados na captura de radicais orgânicos, capacidade redutora e na inibição da oxidação lipídica. Além disso, foi determinada a atividade anti-inflamatória e antioxidante em modelo de edema de orelha, por meio da avaliação da mieloperoxidase (MPO), poder de redução do ferro (FRAP) e enzimas catalase e superóxido dismutase. Em relação à atividade antioxidante, os resultados indicam boa atividade de captura de radicais livres em ambos extratos, sendo que o extrato etanólico mostrou melhor atividade de captura do radical 2,2'-azinobis(3-etilbenzotiazolina-6-ácido-sulfônico) (ABTS). Foi observada boa atividade redutora, principalmente do extrato aquoso, e proteção contra oxidação lipídica de ambos extratos. Esta atividade pode estar associada ao conteúdo dos ácidos gálico e cafeico e dos flavonoides naringenina e quercetina. Já no óleo essencial os compostos γ-3-careno, α-felandreno, β-felandreno, α-pineno e elemol representam mais de 80% dos compostos encontrados e foi observada atividade antioxidante pela captura de radicais livres e pelo potencial de redução. No modelo de edema de orelha, o extrato etanólico diminuiu a formação do edema induzido pelo 12-O-tetradecanoilforbol acetato (TPA) e a atividade da enzima MPO, provavelmente por modular a translocação de neutrófilos. Desse modo, a avaliação dos compostos presentes no fruto de *S. terebinthifolius* indicam que esta pimenta pode representar uma fonte de compostos com importante atividade biológica e assim, deve ser melhor explorada e compreendida, reforçando o papel que as ervas e especiarias tem na culinária e seus possíveis benefícios à saúde.

Palavras-chave: *Schinus terebinthifolius*. Antioxidantes. Inflamação.

LISTA DE SIGLAS

ABTS: 2,2'- azinobis(3-etilbenzotiazolina-6-ácido-sulfônico)

CAT: catalase

COX-2: ciclooxigenase 2

DCNT: doenças crônicas não transmissíveis

DNA: ácido desoxirribonucleico

DPPH: Radical 2,2-difenil-1-picril-hidrazila

ERN: espécies reativas de nitrogênio

ERO: espécies reativas de oxigênio

FRAP: Poder de redução do ferro

GPx: glutationa peroxidase

IL-1β: interleucina 1 beta

IL6: interleucina 6

iNOS: óxido nítrico sintase induzível

Keap1-Nrf2-ARE: Kelch-like ECH-associated protein 1 - nuclear factor erythroid 2-related factor 2 - antioxidant response element

LDL: Lipoproteína de baixa densidade

MPO: enzima mieloperoxidase

NF-κB: fator nuclear kappa beta

NO: Óxido nítrico

ORAC: Capacidade de absorbância do radical oxigênio

PPAR-α: receptor ativado por proliferador de peroxissoma alfa

PPAR-γ: receptor ativado por proliferador de peroxissoma gama

SOD: enzima superóxido dismutase

TBARS: Substâncias reativas ao ácido tiobarbitúrico

TNF-α: fator de necrose tumoral alfa

TPA: 12-O-tetradecanoilforbol acetato

TRAP: Potencial antioxidante reativo total

SUMÁRIO

1 INTRODUÇÃO

A espécie *Schinus terebinthifolius* Raddi, conhecida popularmente como pimenta rosa ou aroeira da praia, é uma especiaria nativa da América do Sul que tem sido utilizada nas regiões trópicas e na Europa (GILBERT; FAVORETO, 2011; ENNIGROU et al., 2018). Diferentes partes da planta, como frutos, caule, casca do caule e folhas da *S. terebinthifolius* são utilizadas na medicina popular devido às suas propriedades farmacológicas como atividade antimicrobiana, antioxidante, anti-inflamatória, antiulcerogênica, anticancerígena, cicatrizante, entre outras (SANTOS; SILVA; CAXITO, 2015).

Esse membro da família Anacardiaceae apresenta na sua composição metabólitos secundários como compostos fenólicos e terpenos, que são associados às suas atividades biológicas (CARVALHO et al., 2013). Os compostos fenólicos atuam como um bioativo natural na proteção contra doenças crônicas devido à sua atividade antioxidante bem discutida na literatura (SHAHIDI; AMBIGAIPALAN, 2015; SHAHIDI; YEO, 2018). Além disso, ácidos fenólicos, flavonoides e terpenos são os principais compostos bioativos que tem relação com as atividades antioxidantes e anti-inflamatórias encontradas em ervas e especiarias (RUBIÓ; MOTILVA; ROMERO, 2013).

Condições como o estresse oxidativo podem contribuir no desenvolvimento de diferentes doenças como câncer, distúrbios metabólicos e disfunções cardiovasculares, devido à lesões em biomoléculas como ácidos nucléicos, lipídios e proteínas (RAHAL et al., 2014; CIANCIOSI et al., 2018). Além do mais, tem a capacidade de atuar no desenvolvimento e propagação da inflamação, e ambos processos oxidativos e inflamatórios estão presentes em doenças como obesidade, diabetes, câncer, doenças neurodegenerativas, entre outras (LUGRIN et al., 2014; BISWAS, 2016).

Portanto, o aprofundamento de estudos com o fruto da espécie, que são escassos na literatura, possibilita a busca por fontes naturais de compostos bioativos que sejam acessíveis ao consumo da população, como a pimenta rosa. Afinal, alimentos que apresentem efeitos atenuantes no estresse oxidativo e na inflamação, ambos processos relacionados com diversas doenças, são de fundamental importância por proporcionarem benefícios à saúde dos

indivíduos, além de enriquecerem sua alimentação trazendo diferentes sabores e possibilidades de combinações em preparações. Então, hipotetiza-se que o fruto da *S. terebinthifolius* possui compostos bioativos que podem retardar ou suprimir o estresse oxidativo além de atenuar a inflamação, que são processos relacionados a várias doenças crônicas não transmissíveis.

2 REVISÃO BIBLIOGRÁFICA

2.1 *Schinus terebinthifolius* Raddi

A família Anacardiaceae apresenta diversas frutas comestíveis como caju (*Anacardium occidentale*), manga (*Mangifera indica*), pistache (*Pistacia vera*) e especiarias como a pimenta rosa ou pimenta brasileira (*S. terebinthifolius*), entre outras espécies com características distintas. Em comum, os membros desta família são conhecidos por serem árvores ou arbustos localizados principalmente em áreas tropicais, subtropicais e temperadas, além disso, suas espécies vem recebendo bastante atenção na busca por substâncias bioativas pelo fato de serem ricas em polifenóis (SCHULZE-KAYSERS, FEUEREISEN, SCHIEBER; 2015). *S. terebinthifolius* (Figura 1A) é uma espécie invasiva e fácil de crescer, que deve ser plantada em pleno sol em solo argiloso, e pode atingir altura de 4,5 m em 2 anos (LORENZI, 2014). Seus frutos (Figura 1B) são drupas aromáticas de coloração vermelha e tamanho de aproximadamente 4 a 5 mm de diâmetro (LORENZI, MATOS; 2008).

A espécie *S. terebinthifolius* é conhecida popularmente como “Brazilian peppertree” e “Florida Holly” (Estados Unidos); “Christmas-berry” (Havaí); “False pepper or Faux poivrier” (Riviera Francesa); "Aroeira da Praia", "Aroeira negra", "Aroeira vermelha", "Aroeira de Minas" (Brasil), "Chichita" (Argentina); "Copal" (Cuba) e "Pimienta de Brasil" (Porto Rico) (MORTON, 1978).

Figura 1- *Schinus terebinthifolius* Raddi (A) e seus frutos (B).

Fonte: Próprio autor, 2016.

Quanto à composição química, *S. terebinthifolius* apresenta consideráveis conteúdos de carotenoides (27,5 μg g^{-1}) e de vitamina C (17,3 mg $100g^{-1}$), além de capsaicina (12,8%) (GOMES *et al.*, 2013). Pesquisas que exploram o perfil fitoquímico ampliam o conhecimento sobre a composição química da família Anacardiaceae e aumentam a compreensão quimiotaxonômica. A presença de flavonoides do tipo 7-*O*-metilado, que é comumente encontrado na família Anacardiaceae, em frutos de *S. terebinthifolius*, por exemplo, é importante para marcar tal fruto no perfil de flavonoides de membros dessa família (FEUEREISEN *et al.*, 2017).

2.2 Compostos bioativos presentes na *S. terebinthifolius*

2.2.1 Compostos fenólicos

Produtos de metabolismo secundário de plantas, os compostos fenólicos são substâncias bioativas presentes em especiarias que possuem atividades antioxidantes, anti-inflamatórias, antimutagênicas e anticancerígenas documentadas experimentalmente (SRINIVASAN, 2014), além disso, estes compostos apresentam propriedades fisiológicas como efeitos antialérgicos, antimicrobianos, antiaterogênicos e cardioprotetores e vasodilatadores (SHAHIDI; AMBIGAIPALAN, 2015).

Os compostos fenólicos são compostos fitoquímicos que possuem na sua estrutura um anel aromático com uma ou mais hidroxila e, frequentemente, apresentam propriedades antioxidantes. Na natureza, os compostos fenólicos estão sob forma livre ou ligados a açúcares e proteínas, compondo dois grandes grupos: o primeiro constituído pelos ácidos fenólicos e flavonoides, e o segundo pelas cumarinas (SOARES, 2002). Os compostos fenólicos são derivados de uma via de biossíntesse comum, incorporando precursores tanto da via do ácido chiquímico quanto da via do acetato-malonato (VATTEM; SHETTY, 2005).

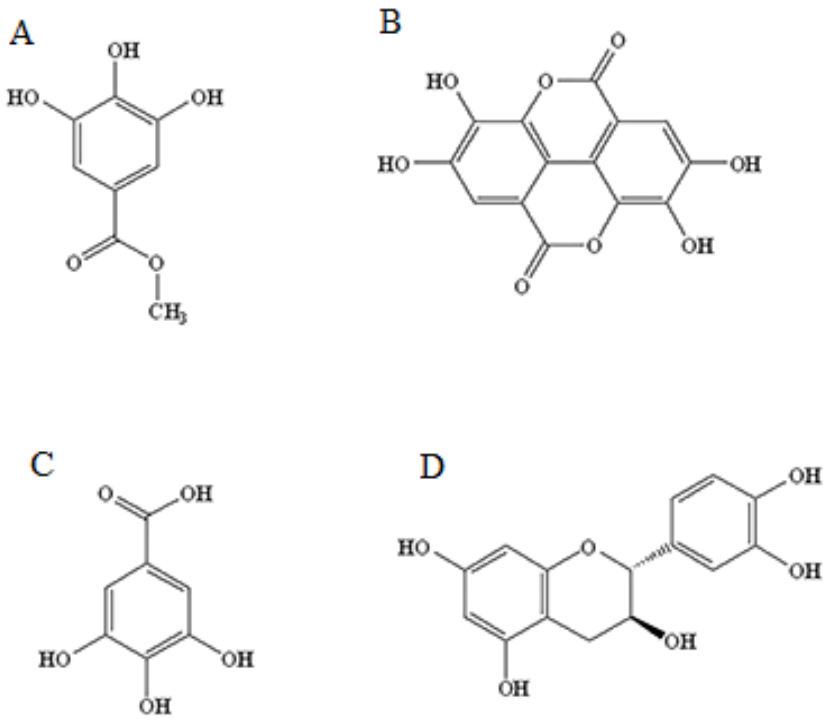
Eles são capazes de atuar sobre o estresse oxidativo e o mecanismo desta ação, supostamente está relacionado com a eliminação direta de radicais livres com grande influência na redução de doenças crônicas como diabetes, câncer e doenças cardiovasculares (SHAHIDI; AMBIGAIPALAN, 2015; LIN et al., 2016).

O conhecimento sobre compostos fenólicos pode revelar seu potencial benefício à saúde e também contribuir para seu uso como fonte de conservantes naturais e antioxidantes,

uma vez que se verificou que estes compostos podem inibir as enzimas lipoxigenase e ciclooxigenase, responsáveis pelo desenvolvimento de rancidez oxidativa (EMBUSCADO, 2015; SCHULZE-KAYSERS; FEUEREISEN; SCHIEBER, 2015).

S. terebinthifolius contém diversos compostos fenólicos tais como flavonoides, metil galato, ácido elágico, ácido gálico e catequina, cujas estruturas químicas estão representadas na Figura 2 (BERNARDES *et al*., 2014; FEUEREISEN *et al*., 2014, 2017; ROSAS *et al*., 2015; SERENIKI *et al*., 2016; NOCCHI *et al*., 2016).

Figura 2 – Estruturas químicas de compostos fenólicos presentes na *S. terebinthifolius*: metil galato (A), ácido elágico (B), ácido gálico (C) e catequina (D).



Fonte: *ChemDraw*® Software.

2.2.2 Terpenos

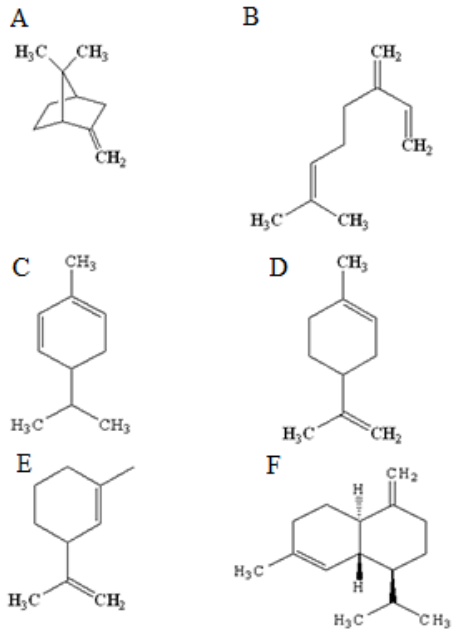
Os terpenos são uma combinação de várias unidades de 5 carbonos-base (C5) chamadas isopreno e podem formar classes com estruturas e funções diferentes. Os

monoterpenos (C10) são formados a partir de duas unidades de isopreno e constituem 90% dos óleos essenciais (RUBIÓ; MOTILVA; ROMERO, 2013).

Diferentes compostos em quantidades distintas são encontrados em várias partes da planta. β-cariofileno (35,2%), α-pineno (28,1%) e germacrênico D (15,5%) representam os principais componentes do óleo essencial de folhas de *S. terebinthifolius*, enquanto o α-pineno (44,9%), germacrênico D (17,6%) e β-pineno (15,1%) estão presentes no óleo essencial de frutos de *S. terebinthifolius* (CAVALCANTI *et al*., 2015).

S. terebinthifolius contém diversos outros terpenos, como α-fencheno, β-mirceno, α-felandreno, limoneno, isosilvestreno, γ–cadineno, e suas estruturas químicas estão representadas na Figura 3 (OLIVEIRA *et al*., 2014; ENNIGROU *et al*., 2011; AFFONSO *et al*., 2012; DANNENBERG *et al*., 2016; GUNDIDZA et al., 2009; BENDAOUD et al., 2010; COLE et al., 2014).

Figura 3 – Estruturas químicas de terpenos presentes na *S. terebinthifolius*: α-fencheno (A), β-mirceno (B), α-felandreno (C), limoneno (D), isosilvestreno (E) e γ–cadineno (F).



Fonte: *ChemDraw*® Software.

2.3 Compostos bioativos e doenças crônicas não transmissíveis (DCNT)

No atual cenário mundial da saúde, as DCNT têm forte impacto na morbimortalidade e qualidade de vida da população (BRASIL, 2011). Segundo dados da Organização Mundial de Saúde, as doenças crônicas não transmissíveis matam 15 milhões de mulheres e homens com idades entre 30 e 70 anos no mundo, sendo que no Brasil 73% das mortes são causadas por tais doenças (WHO, 2017). Além disso, por ano, morrem 2,8 milhões de pessoas devido ao excesso de peso ou obesidade (WHO, 2009) e o risco de desenvolver doenças cardiovasculares e diabetes aumenta consideravelmente com o aumento de peso (WHO, 2002).

Nesse contexto, estratégias para redução dos riscos das DCNT, assim como formas de atenuar seus efeitos metabólicos têm sido estudadas de modo a contribuir para redução da incidência e melhor prognóstico dessas doenças. Alguns estudos demonstraram que o consumo de frutas, verduras e grãos está inversamente relacionado ao risco de desenvolvimento das DCNT (MURSU *et al.*, 2014; YAMADA *et al.*, 2011). De acordo com Zhang et al. (2015), tal repercussão pode estar relacionada à atividade antioxidante de alguns compostos bioativos presentes nesses alimentos, tais como os flavonoides, uma vez que o estresse oxidativo tem estreita relação com a patogênese da maioria das doenças crônicas.

DCNT são doenças de alta prevalência e alto impacto na saúde pública que envolvem alterações em parâmetros inflamatórios e de estresse oxidativo. Diante disso, percebeu-se que compostos como os polifenóis obtinham bons efeitos terapêuticos, devido à ação sinérgica anti-inflamatória e antioxidante, enquanto que agentes antioxidantes ou anti-inflamatórios, quando ingeridos isoladamente, não eram capazes de ter efeitos significativos no tratamento de tais doenças (CARPÉNÉ *et al.*, 2015).

Além disso, os benefícios dos antioxidantes têm sido observados em doenças como câncer, diabetes *mellitus* tipo 2 e doenças neurodegenerativas (DEL RIO *et al.*, 2013). No processo carcinogênico, a atividade antioxidante dos flavonoides parece estimular o sistema imune, eliminando radicais livres e modulando a resposta enzimática e a expressão gênica, de modo a exercer efeito protetor (SAK, 2013; SREELATHA, DINESH, UMA; 2012). No diabetes *mellitus* tipo 2 esse efeito tem sido relacionado ao efeito inibidor dos antioxidantes fenólicos sobre as α-glicosidases e α-amilase, enzimas importantes no metabolismo dos

carboidratos, que, uma vez inibidas, podem reduzir a glicemia pós-prandial, contribuindo para redução de risco e controle do diabetes (APOSTOLIDIS *et al.*, 2011; ZHANG *et al.*, 2015).

Sabe-se que a ingestão de uma dieta rica em antioxidantes traz melhorias nos marcadores de estresse oxidativo e diminuição do dano ao DNA (MITJAVILA et al., 2013), portanto, o consumo habitual de alimentos ricos em antioxidantes é uma forma de combater o estresse oxidativo e a inflamação e, consequentemente, seus efeitos deletérios ao organismo (FRANCISQUETI et al., 2017).

2.4 Estresse oxidativo, espécies reativas e sistema antioxidante

A vida em aerobiose depende de processos oxidativos para obtenção de energia, entretanto o complexo metabólico responsável pela produção de energia pode ser lesado por processos oxidativos. Por esse motivo, os seres aeróbios desenvolveram um complexo sistema antioxidante para controlar a oxidação e reparar possíveis danos causados (JONES, 2006).

O estresse oxidativo pode ser definido como o desequilíbrio entre a produção de espécies reativas e a defesa pelos componentes antioxidantes, em favor dos primeiros (HALLIWELL, 2011). O mesmo compromete a sinalização e controle do sistema de redução/oxidação (redox), desempenhando importante papel no envelhecimento e em diversas condições patológicas, principalmente, nas doenças crônicas não transmissíveis (DCNT) como câncer, diabetes, doenças cardiovasculares, neurodegenerativas e pulmonares (JONES, 2006).

As espécies reativas podem derivar de átomos como oxigênio (ERO) e nitrogênio (ERN) e subdividem-se em dois grupos: radicais livres e espécies não radicalares. Os radicais livres apresentam ausência de um ou mais elétrons na última camada do átomo, deixando elétrons não pareados que buscam equilíbrio oxidando outras moléculas. Por outro lado, as espécies reativas não radicalares são formadas quando dois radicais livres compartilham seus elétrons não pareados, tornando-se mais estáveis, consequentemente, menos reativas (JONES, 2006).

As ERO são produzidas como resultado do metabolismo celular normal (BIRBEN *et al.*, 2012). Em concentrações elevadas, são as principais responsáveis pelos danos causados durante o estresse oxidativo, porém, em concentrações fisiológicas, as ERO atuam na sinalização celular, reações biossintéticas, função na desintoxicação e auxílio do sistema imune (HALLIWELL, 2011; JONES, 2006). As ERO são as mais comuns e tem como principais componentes: superóxido ($O_2^{-\cdot}$), radical hidroxila (•OH) e peróxido de hidrogênio (H_2O_2) (BIRBEN *et al.*, 2012; HALLIWELL, 2011).

Para defesa do organismo dos efeitos do excesso de espécies reativas, existe o sistema de defesas antioxidantes formado por linhas de defesa enzimática e não enzimática que atuam de forma cooperativa e coordenada no organismo. Entre os antioxidantes enzimáticos estão as enzimas superóxido dismutase (SOD), catalase (CAT) e glutationa peroxidase (GPx). Enquanto que os antioxidantes não enzimáticos obtidos pela dieta são representados pelo α-tocoferol (vitamina E), β-caroteno, ácido ascórbico (vitamina C), ácidos fenólicos, flavonoides e outros antioxidantes (LIGUORI *et al.*, 2018). Compostos bioativos com capacidade antioxidante podem ajudar a defender o organismo de danos em ácidos nucléicos, proteínas e lipídeos causados pelas ERO, que são produzidas nas células durante o processo de oxidação (SINGH *et al.*, 2016).

Entre os antioxidantes obtidos pela dieta, o ácido ascórbico (vitamina C) é um importante composto hidrossolúvel encontrado em frutas, verduras e legumes como morango, goiaba, manga, kiwi, pimentas, couve-flor, brócolis, entre outros. Tem a capacidade de modular vias de sinalização redox e fatores de transcrição, podendo exercer efeito protetor no tratamento da sepse, dano relacionado a hipóxia e câncer (HALLIWELL; GUTTERIDGE, 2007; LEONARDUZZI; SOTTERO; POLI, 2010). Tocoferóis e tocotrienóis (vitamina E) são compostos lipossolúveis encontrados em vegetais de folhas verdes, nozes, sementes e óleos vegetais que estão presentes nas membranas celulares e nas lipoproteínas e podem interromper o processo radicalar de peroxidação lipídica (BENZIE, 2003; HALLIWELL; GUTTERIDGE, 2007). Carotenóides são pigmentos lipossolúveis de plantas presentes em vegetais de folhas verdes, frutas e vegetais alaranjados e amarelos (β-caroteno); tomate, goiaba, melancia, mamão (licopeno); espinafre e couve (luteína e zeaxantina) (KRINSKY, JOHNSON; 2005), com eficiente capacidade antioxidante atuando

na varredura do oxigênio molecular singlete e radicais peroxil, e sua interação com outros antioxidantes é mais eficaz do que sua atuação individual (STAHL, SIES; 2003).

As fontes dietéticas de compostos fenólicos são frutas, legumes, chás, vinho, produtos de cacau (REDAN *et al.*, 2016), ervas e espécies aromáticas (GONÇALVES *et al.*, 2017). Tais compostos compreendem diversos efeitos biológicos e podem ser divididos em duas categorias. A primeira está associada à relação estrutura-atividade, devido à presença do anel fenólico e hidroxilas, atuando como antioxidantes efetivos no sequestro de radicais livres e na inibição da oxidação em cascata e, dessa forma, inibindo reações oxidativas desses radicais com moléculas biológicas, como: lipídios, carboidratos, proteínas e DNA (ácido desoxirribonucleico) (VATTEM, SHETTY; 2005). O segundo e mais significativo mecanismo de ação se dá em consequência de sua capacidade em modular a fisiologia celular, tanto em níveis moleculares quanto bioquímicos/fisiológicos. Devido a sua estrutura ser similar a inúmeras moléculas biológicas sinalizadoras e efetoras, os compostos fenólicos são capazes de participar dos processos de repressão/indução da expressão gênica ou na ativação/desativação de proteínas, enzimas e fatores de transcrição de vias metabólicas (YEH; YEN, 2006a; b; YEH; CHING; YEN, 2009).

Os mecanismos antioxidantes dos compostos fenólicos incluem a ativação e/ou aumento na atividade e/ou expressão das enzimas antioxidantes superóxido dismutase (SOD), catalase (CAT) e glutationa peroxidase (GPx) via complexo Kelch-like ECH-associated protein 1 - nuclear factor erythroid 2-related factor 2 - antioxidant response element (Keap1-Nrf2-ARE) (BATISTA-GONZALEZ *et al.*, 2012; MANCINI-FILHO *et al.*, 2009; SILVA *et al.*, 2011; ZENKOV *et al*., 2016).

Diferentes abordagens podem ser utilizadas para testar atividade antioxidante em alimentos e sistemas biológicos. Estes métodos podem ser baseados na captura dos radicais 2,2-difenil-1-picril-hidrazila (DPPH), 2,2'- azinobis(3-etilbenzotiazolina-6-ácido-sulfônico) (ABTS) ou óxido nítrico (NO), na capacidade de redução do metal ferro (FRAP), na quantificação de produtos formados durante a peroxidação de lipídios (co-oxidação do β-caroteno, substâncias reativas ao ácido tiobarbitúrico - TBARS, oxidação do LDL), na captura do radical peroxila - capacidade de absorbância do radical oxigênio (ORAC) ou potencial antioxidante reativo total (TRAP), na captura do radical hidroxila (método de

desoxirribose), entre outros. Os diferentes mecanismos de ação dos antioxidantes justifica o emprego de diversas metodologias a fim de medir diferentes características do antioxidante (CRAFT *et al.*, 2012).

2.5 Compostos bioativos na inflamação

O estado de saúde do indivíduo pode afetar significativamente a maneira como os compostos fenólicos são absorvidos, metabolizados e transportados para os tecidos alvo, o que implica diretamente na biodisponibilidade desses compostos. Estudos mostram que condições como a obesidade ou diabetes podem alterar a absorção e excreção dos compostos fenólicos, e isso se dá possivelmente devido ao aumento do estado inflamatório a partir de quantidades aumentadas do tecido adiposo ou concentrações elevadas de glicose no plasma (REDAN *et al.*, 2016).

Ervas culinárias e especiarias podem contribuir de forma significativa na dieta de indivíduos por meio de sua atividade anti-inflamatória, a partir de diferentes mecanismos como ativação de receptor ativado por proliferador de peroxissoma alfa (PPAR-α) e receptor ativado por proliferador de peroxissoma gama (PPAR-γ), inibição de fator nuclear kappa beta (NF-κB) e aumento da expressão de citocinas anti-inflamatórias (JUNGBAUER; MEDJAKOVIC, 2012).

Além disso, compostos bioativos como os compostos fenólicos podem atuar na inflamação a partir de mecanismos como a supressão de enzimas pró-inflamatórias ciclooxigenase 2 (COX-2) e óxido nítrico sintase induzível (iNOS) (TSAI *et al*., 2017). Além de serem também eficazes na redução de citocinas pró-inflamatórias como fator de necrose tumoral alfa, interleucina 1 beta e interleucina 6 (TNF-α, IL-1β e IL6), do infiltrado celular e da atividade da enzima mieloperoxidase (MPO) (MÜLLER *et al*., 2016). Portanto, o consumo diário de fontes de compostos que atenuam a inflamação contribui para a neutralização da mesma.

As atividades quimiopreventivas e anti-inflamatórias de *S. terebinthifolius* estão associadas com os efeitos antioxidantes dos compostos fenólicos. Estes também modulam a fagocitose esplênica e aumentam a taxa de apoptose, o que, consequentemente, diminui o

risco de desenvolver câncer, além de auxiliar na hepatoproteção e outras doenças nas quais o processo inflamatório está envolvido (FEDEL-MIYASATO *et al.*, 2014).

Entre os modelos existentes para investigar o efeito anti-inflamatório de compostos, está o edema de orelha induzido por 12-O-tetradecanoilforbol acetato (TPA). Tal método é amplamente utilizado para a investigação da atividade anti-inflamatória na inflamação aguda e a aplicação tópica de TPA na pele do animal pode gerar respostas inflamatórias como aumento da MPO, aumento das concentrações de citocinas inflamatórias (IL-1β, TNF-α), aumento da expressão da COX-2, aumento da atividade de NF-κB (CINATL *et al*., 2001; HWANG *et al*., 2009; OLIVEIRA *et al*., 2017).

Portanto, a partir de uma extensa revisão da literatura, baseando-se nas principais atividades biológicas encontradas para a espécie *S. terebinthifolius*, buscou-se estudar o perfil fitoquímico de extratos e óleo essencial dos frutos, bem como as propriedades antioxidantes e anti-inflamatória.

3 OBJETIVOS

3.1 Objetivo geral

Identificar e quantificar os compostos presentes nos extratos e no óleo essencial do fruto de *S. terebinthifolius* e avaliar as atividades antioxidante e anti-inflamatória.

3.2 Objetivos específicos

- ✓ Realizar uma revisão da literatura de estudos a respeito da composição e atividades biológicas da espécie *S. terebinthifolius*;
- ✓ Determinar o teor de compostos fenólicos totais e de flavonoides nos extratos aquoso e etanólico do fruto de *S. terebinthifolius*;
- ✓ Determinar o teor de compostos no óleo essencial do fruto de *S. terebinthifolius*;
- ✓ Avaliar a atividade antioxidante dos extratos e do óleo essencial, utilizando os métodos de captura de radicais livres (DPPH, ABTS e NO), capacidade redutora (FRAP) e inibição da oxidação lipídica (β-caroteno e TBARS);
- ✓ Avaliar as atividades anti-inflamatória e antioxidante em modelo de edema de orelha, por meio da análise da atividade de mieloperoxidase, FRAP e enzimas catalase e superóxido dismutase.

4 RESULTADOS E DISCUSSÃO

ARTIGO I

Bioactive compounds from *Schinus terebinthifolius* Raddi and their potential health benefits: a review.

(Artigo submetido e nas normas da revista Biomedicine & Pharmacotherapy)

Bioactive compounds from *Schinus terebinthifolius* Raddi and their potential health benefits: a review

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Highlights

- *Schinus terebinthifolius* is commonly identified as Brazilian pepper.
- Bioactive compounds found in different parts of *S. terebinthifolius*.
- Phenolics enhanced the biological activities of *S. terebinthifolius*.
- It shows antimicrobial, wound-healing, anti-inflammatory, and antioxidant activity

Abstract

Schinus terebinthifolius Raddi contains numerous phenolic compounds and terpenes. The bioactive compounds found in the root bark, stem bark, leaves, and fruits of *S. terebinthifolius* have been identified and studied extensively. We carried out a literature review of all studies limited to *S. terebinthifolius* plant species published in Embase, PubMed, Scopus, and Web of Science from its beginning to July 2018. We identified the bioactive compounds from different parts of *S. terebinthifolius* and described the main activities of this species i.e., antimicrobial, wound-healing, anti-inflammatory, and antioxidant. This review also summarizes the health benefits of natural substances characterized and isolated from *S. terebinthifolius*.

Keywords: *Schinus terebinthifolius*; phenolic compounds; terpenes; biological activity.

1 Introduction

Spices and culinary herbs are generally used for flavor and fragrance in order to enhance food palatability, but have also played an important role in preserving human health and well-being since ancient times [1]. Common spices such as pepper and turmeric change the color, appearance, and taste of food preparations, in addition to promoting human health and fighting diseases [2].

Schinus terebinthifolius Raddi, a spice popularly known as Brazilian pepper or pink pepper, is a flowering plant species of the Anacardiaceae family and is found along the Brazilian coast from Ceará to Rio Grande do Sul. This plant species is also present in regions of the United States and is widely distributed in South America [3]. The species is invasive and easy to grow, must be planted in full sun on clay soil, and can reach a height of 4.5 m in 2 years [4].

Different parts of the plant, such as fruits, seeds, leaves, and stem bark are commonly used for medicinal purposes for years [5]. In culinary practice, it is widely used in French cuisine, due to the essential oil found in its fruits. In addition, they are used in syrups, vinegars, and beverages in Peru, and in wines in Chile [6,7].

The medicinal importance of spices was widely recognized in folk medicine and recent scientific literature has confirmed their health benefits to consumers [8]. Furthermore, chemical constituents found in spices have antimicrobial properties against microorganisms that alter food quality and shelf life [9]. The antimicrobial and antioxidant activities reported in previous literature can rationalize the use of this particular spice for preservation in the food industry [5,10].

Hence, the present study aims to review the information about the chemical constituents of *S. terebinthifolius* Raddi, its potential application as a bioactive compound in food, and its health benefits.

2 Search strategies

This review was carried out via a specialized search across four databases (Embase, PubMed, Scopus, and Web of Science) databases through July 2018, using the keyword "*Schinus terebinthifolius*". All titles, abstracts, and full-texts of the articles were reviewed by the authors of this study. Studies on bioactive compounds from *S. terebinthifolius* (Fig. 1) and associated beneficial effects on human health were included. Review articles, abstracts, case reports and activities that are not interest to this review were excluded.

Data from chosen reports were extracted by four study authors using predefined selection criteria and the assessments were approved by all authors. The data extracted included information related to the part of the plant, methods of extraction, characterized compounds, mechanism of action, and biological activities. The procedure followed during article realization is presented in Fig. 2. Initially, 1075 citations were electronically identified through our survey. After eliminating duplicates, we proceeded with critical analysis of 508 articles, titles, and abstracts. However, only 79 articles were chosen for a full-text review and finally, only 58 articles fitted the inclusion criteria and satisfied the objectives of this study.

3 Bioactive compounds

For several years, spices have been used in folk medicine for the treatment of distinct diseases because of the bioactive compounds they contain [11]. Antioxidant phytochemicals are capable of disrupting or suppressing oxidative stress, thereby preventing chronic diseases

induced by free radicals. Herbs and spices are considered important sources of natural antioxidants and have lately received increasing research attention [12].

This section focuses on some bioactive compounds present in the species *S. terebinthifolius* (Table 1). The phenolic compounds and terpenes have received the most attention, as they are responsible for the beneficial health properties of *S. terebinthifolius*.

3.1 Phenolic compounds

Phenolic compounds are the most known antioxidants in the literature, they are predominantly present in fruits, vegetables, grains and spices, and are generally related to plant defense. They originate from the secondary metabolism of plants through two metabolic routes: the shikimic acid route, that produces phenylalanine, which eliminates an ammonia molecule, forming the cinnamic acid that synthesizes the phenolic compounds of the plants; and the route of malonic acid, a route for the synthesis of phenolic compounds in fungi and bacteria. The four main families are classified as flavonoids, phenolic acids, stilbenes and lignans [13–15].

The species *S. terebinthifolius* contains numerous phenolic compounds such as ethyl gallate, quercitrin, myricetrin, myricetin, methyl gallate, caffeic acid, syringic acid, p-coumaric acid, ellagic acid, gallic acid, and catechin [10,16–25]. Recently, anthocyanins and bioflavonoids have been identified in extracts of the fruits of this plant [19]. It is interesting to note that fruit maturation may interfere in its composition. A study with immature, halfmature and full mature fruits, found that there is a highest total phenol contents in full mature fruits and highest total flavonoid contents in halfmature fruits [26].

Some structures are shown in Fig. 3 and the contents of the phenolic compounds found in different parts of *S. terebinthifolius* as well as the type of extraction and technique used to characterize those chemical constituents are shown in Table 1.

3.2 Terpenes

Terpenes are combinations of various units of 5 carbon bases (C5) known as isoprene which can form different types of compounds with different structures and functions. The biosynthesis of these compounds includes the repeated addition of isopentenyldiphosphate to form specific precursors of the various classes of terpenes, besides the action of synthetases to form the terpene skeleton and then a secondary enzyme acts by modifying the skeleton through redox reactions, responsible for the attribution of functional properties of these compounds. The class of monoterpenes (C10) is characterized by having two units of isoprene and it is present in 90% of essential oils [27].

The composition and number of terpenes can be different in each part of the plant, β-caryophyllene (35.2%), α-pinene (28.1%), and germacrene D (15.5%) represent the major components from *S. terebinthifolius* leaves essential oil, while α-pinene (44.9%), germacrene D (17.6%), and β-pinene (15.1%) are present in *S. terebinthifolius* fruits essential oil [28]. In addition, *S. terebinthifolius* contains others terpenes, such as α-fenchene, β-myrcene, α-phellandrene, limonene, isosylvestrene, and γ-cadinene and some structures are shown in Fig. 4 [6,29–35].

Besides that, the extraction methods and type of solvent used may influence the compounds found in the sample. As can be seen in the study that analyzed the composition of essential oil, acetone and n-hexane extracts from *S. terebinthifolius* ripened fruits and

found that the major components of the essential oil were α-pinene and α-phellandrene, of the acetone extract were oleic acid, α-phellandrene and δ-cadinene and the major methyl esters of fatty acids of the n-hexane extract were oleic and palmitic [36].

4 Biological activities

4.1 Antimicrobial activity

Compounds obtained from natural sources such as *S. terebinthifolius* have great potential as antimicrobial agents (Table 2). The majority of the studies evaluating the antimicrobial activity of this species were carried out with the leaves of the plant, which showed a significant inhibitory effect on the growth of tested microorganisms [10,22,34,36–42,43,44]. Antibacterial and antifungal activities of crude extract, leaf extract, and *S. terebinthifolius* leaf lectin were evaluated by determining the minimal inhibitory (MIC), bactericidal (MBC), and fungicidal (MFC) concentrations. The leaf extract had an inhibitory effect on *E. coli, P. mirabilis*, and *S. aureus* growth and no effect on *K. pneumoniae, P. aeruginosa,* and *S. enteritidis*, while *S. terebinthifolius* leaf lectin was active against all tested bacteria. In the antifungal assay, both the leaf extract and *S. terebinthifolius* leaf lectin inhibited the growth of *C. albicans* [40].

The antimicrobial activity and chemical composition of *S. terebinthifolius* leaf extract and essential oil was investigated, and the leaf extract presented a strong activity against *S. aureus* and *E. coli* and moderate activity against *C. albicans*, while only *C. albicans* was sensitive to the essential oil. According to the authors, the antimicrobial activities of extracts and fractions of *S. terebinthifolius* leaves were related to the phenolic compounds and flavonoids present in the plant [22]. In another study, *S. terebinthifolius* showed antifungal

activity against *C. albicans*, and it is suggested that the Brazilian pepper tree inhibits the formation of the fungal cell wall [46].

In general, analysis of the antimicrobial activity of *S. terebinthifolius* fruits against gram-positive and gram-negative bacterial strains revealed similar results. The antimicrobial effect of the essential oils from green and mature fruit from *S. terebinthifolius* was evaluated and all gram-positive bacteria tested were sensitive, while three of the six gram-negative bacteria tested were resistant to both essential oils [30]. In another study, antibacterial activity of the essential oil obtained from *S. terebinthifolius* ripe fruits was evaluated against wild strains of hospital origin and the gram-positive species were more sensitive to the essential oil than the gram-negative species were, which could be explained by the lower structural complexity of their cell walls [33].

Besides this, another study using the essential oils of *S. terebinthifolius* immature, half-mature and mature fruits against two gram-positive and two gram-negative bacterial strains, found the gram-positive strains were particularly sensible to the essential oils from the mature fruits, while the gram-negative strains were less susceptible to all examined essential oils. And this resistance of gram-negative bacteria was mostly attributed to the occurrence of a very restrictive lipopolysaccharides containing in outer membrane [26].

Some factors that may influence the inhibition of the microorganism are the extraction methods and type of solvent used. A study analyzed the action of essential oil, acetone and n-hexane extracts from *S. terebinthifolius* ripened fruits against the growth of *Acinetobacter baumannii*, *Bacillus subtilis*, *Escherichia coli*, *Micrococcus flavus*, *Pseudomonas aeruginosa*, *Sarcina lutea*, and *Staphylococcus aureus*. As a result, it was observed that the essential oil showed good activity against the growth of *S. aureus* and *P.*

aeruginosa, the acetone extract showed wide activity against the studied bacterial pathogens, while the n-hexane extract showed weak antibacterial activity [36].

A study that evaluated not the whole fruit, but its peel, showed that the methanol extract, flavonoid fraction, and isolated apigenin from fruit peels inhibited the growth of *Mycobacterium bovis* BCG and the authors suggested that flavonoids were responsible for this action [16]. Another study carried out with fruit ethanolic extract showed no inhibition of gram-positive *E. faecalis* [39].

The antiviral effect of *S. terebinthifolius* was studied by Nocchi *et al*. (2016), and the anti-HSV-1 activity was tested using the crude hydroethanolic extract from stem bark, its fractions, and isolated compounds. The results showed that the extract contained flavan-3-ols and had greater anti-HSV-1 activity than did its fractions and isolated compounds.

In the case of human studies, a 15-day treatment with *S. terebinthifolius* tincture for removable denture wearers with clinical diagnosis of type II denture stomatitis and presence of candidosis associated with denture use resulted in remission of the *Candida spp* infection [47]. Another treatment with a pepper tree extract gel in women diagnosed with bacterial vaginosis had a lower cure rate than that obtained with metronidazole gel, and side effects were infrequent and non-severe in both treated groups [48].

Studies demonstrate that different parts of the *S. terebinthifolius* species have proven antimicrobial activity, which is probably due to bioactive compounds such as phenolic compounds, including the flavonoids present in the plant. Furthermore, both essential oil and extracts or even isolated substances obtained from different parts of the plant have activity against bacteria, fungi, and viruses. It is worth noting that in addition to *in vitro* studies, human studies have also been carried out, and that they have shown favorable results. The

knowledge obtained concerning antimicrobial activity in *S. terebinthifolius* makes possible its use due to its potential benefits for the quality of the food and for the human health.

4.2 Healing activity

Studies to evaluate the healing action of *S. terebinthifolius* were carried out in rats and predominantly using hydroalcoholic extract from the plant's inner bark, as shown in Table 3. The use of essential oil from leaves in ointment form accelerated the wound-healing process by various mechanisms, such as increasing mast cell concentration, promoting skin wound contraction, increasing the number of blood vessels and collagen fibers deposition in rats [49–51] while topical use of the hydroalcoholic extract delayed there epithelization of skin wounds [52].

Following injury and suture in the stomach, the healing process in rats was accelerated by the oral use of hydroalcoholic extract from the inner bark [53,54], however, its intraperitoneal use did not affect the healing process [55].

Studies focusing on the healing activity of hydroalcoholic extracts of *S. terebinthifolius* report a favorable effect on the healing process of bladder cystotomies, colonic anastomosis, abdominal wall cut, and cecotomy and cecorrhaphy [56–59].

The majority of the studies indicates beneficial effects on the use of both essential oil and extracts of *S. terebinthifolius* for healing purposes, although they do not deep into the mechanisms of action involved. Therefore, despite the need for further studies, it is perceived that cicatrizant activity is a potential biological property of *S. terebinthifolius*.

4.3 Anti-inflammatory activity

In recent years, interest in the search for natural compounds with anti-inflammatory activity has grown, considering the adverse effects presented by anti-inflammatories

available in the market. Accordingly, plants, especially herbs and spices, have gained interest and many researches using different parts of the plant such as the bark, inner bark, leaves, and fruits have revealed a diversity of compounds with promising anti-inflammatory activity, both in animal models and in human preclinical trials [60].

Studies demonstrating the anti-inflammatory properties of the species *S. terebinthifolius* are shown in table 4. *S. terebinthifolius* leaves are rich in secondary metabolites and can reduce inflammation in mice. Methanolic extract reduces ear edema and leukocyte migration in the air pouch model [23] and carrageenan-induced paw oedema [61], and the anti-inflammatory activity of compounds present in leaves, extract and essential oil, may be associated with the reduction of neutrophil and macrophage migration and the production of inflammatory cytokines, as observed in the zymosan-induced arthritis model [21] and healing skin wound [51].

Nunes-Neto *et al*., (2017) also demonstrated that ethanolic extract from the stem bark reduces paw edema in a dose-dependent manner in rats similar to hydroxyzine [62].

The anti-inflammatory and chemopreventive activities of *S. terebinthifolius* are associated with the antioxidant effects of secondary metabolites. These compounds also modulate splenic phagocytosis and increase the rate of apoptosis, which consequently decreases the risk of developing cancers, besides helping in hepatoprotection and other diseases where the inflammatory process is involved [23].

S. terebinthifolius fruits contain compounds with promising anti-inflammatory activity, flavonoids and apigenin, which are present in the methanolic extract and fraction, respectively, as well as monoterpenes present in the essential oil. The anti-inflammatory activity of α-pinene, one of the terpenes found in this species has been described in the

literature, and the mechanism of action involving this activity seems to include reduction of the activity of mitogen-activated protein kinases (MAPKs), NF-kB and IL-6, TNF-α and NO production in lipopolysaccharide-induced macrophages [63,64].

Formagio *et al*., (2011) observed the anti-inflammatory activity of the essential oil from the fruit in models of inflammation induced by carrageenan and complete Freund's adjuvant. The extract and fractions seem to control inflammation by modulating nitric oxide production by macrophages and by attenuating oxidative stress. This activity may be related to the presence of apigenin, the major active compound [16].

Human trials have also demonstrated the important effects of this species on reducing gingival inflammation in children and patients with chronic gingivitis when used as a mouthwash [66,67].

It is probable that these compounds exhibit anti-inflammatory effects by regulating inflammatory mediators, enzymes, and genes, and thus change cellular functions and attenuate inflammation. So, further studies on the mechanism of action of the *S. terebinthifolius* species are needed, and specifically about the biological properties of the fruit, since it is the comestible part of the plant and may possibly contribute to health maintenance and reduction of chronic diseases in which inflammation is an important component.

4.4 Antioxidant activity

Reactive oxygen species (ROS) produced in the cells during the oxidation process may cause damage to nucleic acids, proteins, and lipids, and bioactive compounds with antioxidant capacity can help to defend the organism from these oxidative reactions [68]. Phytochemicals such as polyphenols derived from plants act at the cellular level to regulate

oxidative stress, possibly activating initially a mild oxidative stress to induce a positive and beneficial response in the cells [69].

The knowledge obtained regarding polyphenols in *S. terebinthifolius* revealed their potential benefits to health and to food quality. It has been reported that these compounds could inhibit the enzymes lipoxygenase and cyclooxygenase, which are responsible for the development of oxidative rancidity [70,71].

Table 5 contains a summary of the studies that describe the antioxidant activity found in this search for the *S. terebinthifolius* species. It is important to consider that the extraction methods and type of solvent used affect the antioxidant activity of *S. terebinthifolius*. Ultrasound assisted extraction yielded a higher flavonoid content, while extraction by the maceration method resulted in a higher content of total phenolic compounds [22]. Comparison between extracts obtained from the same tissues, but via different extraction methods, suggests that the antioxidant activity is enhanced for samples obtained using the Soxhlet apparatus [39]. The dichloromethane extract and essential oil contained lower concentrations of phenolic contents in comparison with the ethanol extract, which showed better antioxidant activity [10].

Several approaches shave been used to test antioxidants in food and biological systems, different mechanisms of action of antioxidants justify the use of several methodologies in order to measure the different characteristics of the antioxidant [13]. The ability to scavenge free radicals represented by DPPH and ABTS assays were the principal methods used to investigate the antioxidant activity of *S. terebinthifolius*.

The DPPH method was used to determine the antioxidant activity of the essential oil, ethanol, methanol, dichloromethane, acetone, n-hexane and ethyl acetate extracts, and

isolated compounds found in different parts of *S. terebinthifolius* such as the leaves, fruit peels, fruits, stem, and stem bark [10,16,20,22,24,36,39,72]. There are different methodologies capable of testing the antioxidant activity of the same sample, which can generate similar results or not, so it is important to evaluate the antioxidant capacity with more than one assay. In a study carried with the essential oil from *S. terebinthifolius* red berries, it exhibited a strong antioxidant activity involving electron transfer in the ABTS assay, however showed a weak free radical scavenging activity in the DPPH assay [32]. While in another study with the methanolic extract from *S. terebinthifolius* leaves, the extract presented potent antioxidant activity, attributed to the compounds found, in both DPPH, ABTS and β-Carotene/linoleic acid assay [61].

Compounds from the plant's secondary metabolism, such as phenolic compounds found in herbs and spices, have an important influence on human health through their significant antioxidant activities [14,73]. *In vitro* results suggest that the antioxidant and biological activities of *S. terebinthifolius* are related to its chemical composition, especially to the concentration of phenolic content including flavonoids, and consequently to the structure–activity relationship of these compounds [10,16,20,22,32]. This explains the efficacy of the extracts compared with the essential oil, where mainly terpenes are found. As can be seen in a study comparing the antioxidant activity by the DPPH assay in essential oil and methanolic extract of *S. terebinthifolius* fruits, which found that the extract presented greater radical scavenging activity than the essential oil [26]. In addition, another research, done with essential oil of *S. terebinthifolius* leaves and twigs, found high amount of monoterpene hydrocarbons and low DPPH radical scavenging activity [38].

The neuroprotective effect of the *S. terebinthifolius* stem bark extract on behavior activity and oxidative stress in a model of Parkinson's disease in rats was investigated. The authors showed a neuroprotective effect presumably mediated through its antioxidant activity, demonstrated by the inhibition of lipid peroxidation in rats [24].

Despite the data already present in the literature on the antioxidant effects of *S. terebinthifolius*, further research is needed to investigate this species as a potential dietary source of antioxidant compounds with positive health effects.

Toxicity

In view of several biological activities and consequently different uses for *S. terebinthifolius* species, it is considered important to evaluate their toxicity. In an 83-day chronic treatment with bark decoction performed in male rats, decreased numbers of red blood cells and hemoglobin was observed. The plant showed moderate toxicity after acute and chronic treatment by gavage, in addition, bone malformations were induced in fetuses, and a slight delay in the recovery time of the ovoid reflex was observed in pups of rats treated with *S. terebinthifolius*. However, this treatment did not cause anatomopathological changes and the mating and fertility capacity was not affected [74]. On the other hand, another study that evaluated the toxicity of *S. terebinthifolius* fruit ethanolic extract showed that it had no toxic effect on the mice that received the limit dose (5 g.kg -1), about 2,500 times higher than which is generally used as a condiment in a 14-day treatment [75].

5 Future considerations

In the present work, we have reviewed the bioactive compounds found in *S. terebinthifolius* Raddi, focusing on phenols and terpenes, as well as various biological

activities of plant extracts and essential oils, including antimicrobial, healing, anti-inflammatory, and antioxidant activities.

Considering that some studies have shown positive results and revealed potential health benefits for these activities through the composition of *S. terebinthifolius*, further studies are necessary, since scientific evidence is still incipient and these are necessary to better elucidate the mechanisms of action and provide additional evidence.

The majority of studies were conducted in warm regions of Brazil, which may favor the concentration of these bioactive compounds, since the plant needs to adapt to environmental conditions and the production of phenolic compounds is one of the mechanisms for such action. The plant is extensively disseminated in folk medicine, is a promising antioxidant source in diet, and can be widely used in gastronomy. In Brazil, the Health Ministry announced a list of 71 species of Medicinal Plants of interest for the Single Health System, among them the *S. terebinthifolius*, which dried stem bark could be used by the population due its anti-inflammatory and healing potential.

Thus, the extensive survey carried out in this review allows us to propose that while the phytochemical analysis of the species is at an advanced stage, promising biological approaches require further studies to investigate the pharmacological and pharmacokinetic properties as well as safety of this plant. Moreover, *S. terebinthifolius* is widely used in cooking yet few studies have combined its use as a functional food and as adjuvant tool with other therapies. A broader biological engagement with *S. terebinthifolius* will enable its application in the development of biotechnological products and, more importantly, better use of this spice by the biotechnology, pharmaceutical, and food sectors.

Conflict of interest

The authors declare no competing financial or personal interest.

Acknowledgements

This study was financed in part by the Conselho Conselho Nacional de Desenvolvimento Científico e Tecnológico – Brasil (CNPq), the Fundação de Apoio à Pesquisa e a Inovação Tecnológica do Estado de Sergipe (Fapitec/SE) - Brasil, the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES - Finance Code 001), and the Financiadora de Estudos e Projetos - Brasil (FINEP). And is part of N. B. Macedo's Master Thesis, which was present to Post-Graduate Program in Nutrition Sciences (PPGCNUT), Federal University of Sergipe, Brazil.

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Table 1 – Compounds found in *S. terebinthifolius* according to part, preparation and technique used

Authors, year, Country	Part	Preparation	Technique used	Compounds found
Ceruks *et al*., 2007. Brazil (SP)	Leaves	Ethanolic extract	NMR	5 phenolic compounds: ethyl gallate, methyl gallate, quercitrin, myricetrin and myricetin
Farag, 2008. Egypt	Leaves	Aqueous acetone extract	HPLC	2 quinic acid esters: 5-O-caffeoylquinic acid and 5-O-coumaroylquinic acid; 3 myricetin glycosides: myricetin 3-O-α-L-rhamnopyranosyl (1’’’→6’’)β-D-galactopyranoside, myricetin 3-O-β-D-glucuronide and myricetin 3-O-β-D-galactopyranoside; 1,6-digalloyl-β-D-glucose and (+)- catechin
Santos *et al*., 2009. Brazil (RS)	Leaves, Fruit	Essential oil	GC, GC-MS	29 compounds identified. Sesquiterpene and monoterpene hydrocarbons. Limonene, germacrene D, cadinene and myrcene
El-Massry *et al*., 2009. Egypt and California	Fresh leaves	Essential oil, dichloromethane extract, ethanolic extract	GC, GC-MS	Essential oil: monoterpenes, sesquiterpenes, oxygenated monoterpenes, oxygenated sesquiterpenes, cis-β-terpineol, (E)-caryophyllene, β-cedrene and citronellal Ethanol extract: caffeic acid, syringic acid, coumaric acid, ellagic acid, gallic acid and catechin
Gundidza *et al*., 2009. South Africa	Fresh leaves	Essential oil	GC, GC-MS	Sabinene, α-pinene, α-phellandrene, β-pinene, terpinene-4-ol, trans-β-ocimene and myrcene
Bendaoud *et al*., 2010. Tunisia and France	Berries	Essential oil	GC-FID, GC-MS	α-phellandrene, β-phellandrene, α-terpineol, α-pinene, β-pinene, p-cymene, γ –cadinene
Johann *et al*., 2010. Brazil (MG)	Leaves and stems	Hexane and dichlomethane fractions	HPLC	Schinol, a new biphenyl compound, namely, 4’-ethyl-4-methyl-2,2’,6,6’-tetrahydroxy[1,1’-biphenyl]-4,4’-dicarboxylate, quercetin and kaempferol

Ennigrou *et al*., 2011. Tunisia and France	Leaves	Essential oil	GC-MS	Monoterpenes hydrocarbons. α-phellandrene, β-phellandrene, α-pinene and β-myrcene
Formagio *et al*., 2011. Brazil (MS)	Fruits	Essential oil	GC-MS	Monoterpenes
Affonso *et al*., 2012. Brazil (ES)	Fruits	Essential oil	GC, GC-MS	22 components, including mono and sesquiterpenes. α-fenchene, β-pinene, β-myrcene, α-phellandrene, limonene and isosylvestrene
Santana *et al*., 2012. Brazil (MG)	Leaves	Essential oil	GC-FID, GC-MS	49 constituents identified. Germacrene D, bicyclogermacrene, β-pinene and β-longipineneas
Sartorelli *et al*., 2012. Brazil (SP and MG)	Ripe fruits	Essential oil	GC, GC-MS	Monoterpenes and sesquiterpenes
Bernardes *et al*., 2014. Brazil (RJ)	Fruit peels	Methanolic extract	HPLC	Flavonoids
Cole *et al*., 2014. Brazil (ES)	Ripe fruit	Essential oil	GC-MS	17 components. Monoterpenes and sesquiterpenes. Major monoterpenes: γ-3-carene, limonene, α-phellandrene and α-pinene. Major sesquiterpene: trans-caryophyllene
Fedel-Miyasato *et al*., 2014. Brazil (MS)	Leaves	Methanolic extract	LC	Caffeic and p-coumaric acids, quercetin, luteolin and apigenin
Feuereisen *et al*., 2014. Germany	Exocarp	Ethanol/water/acetic acid extracts	UHPLC-DAD-MS/MS, 2D NMR	Anthocyanins (7-*O*-methylpelargonidin 3-*O*-*β*-D-galactopyranoside), biflavonoids (I3',II8-biapigenin (amentoflavone), I6,II8-biapigenin (agathisflavone) and II-2.3-dihydro-I3',II6-biapigenin), gallic acid, hydrolyzable tannins (galloyl glucoses, galloyl shikimic acids)
Oliveira *et al*., 2014. Brazil (SE)	Seeds, leaves	Essential oil	GC-MS	Mono and sesquiterpenes. ρ-menth-1-en-9-ol, α-tujene, β-pinene, camphene, α-fenchene, terpinen-4-ol acetate, bornila acetate, caryophyllene, terpinen-4-ol, Germacren-D, δ-cadinene, hedicariol, α-gurjunene, α-eudesmol, β-eudesmol

Cavalcanti *et al*., 2015. Brazil (RJ)	Leaves, Fruit	Essential oil	GC-MS	Major components Leaves: β-caryophyllene, α-pinene, germacrene D Major components Fruit: α-pinene, germacrene D, β-pinene
Rosas *et al*., 2015. Brazil (RJ)	Leaves	Hydroalcoholic extract	HPLC	Gallic acid, methyl gallate and pentagalloylglucose
Dannenberg *et al*., 2016. Brazil (RS)	Green and mature fruits	Essential oil	GC-MS	β-myrcene, β-cuvebene and limonene
Ennigrou *et al*., 2016. Tunisia	Immature, halfmature and full mature fruits	Essential oil, methanolic extract	GC–MS, Folin–Ciocalteu assay and $AlCl_3$ colorimetric method	Oil-main compounds: α-phellandrene, α-pinene and limonene. Methanolic extract: highest total phenol contents in full mature fruits and highest total flavonoid contents in halfmature fruits
Serenik *et al*., 2016. Brazil (PE)	Stem bark	Ethanol extract	HPLC	Gallic acid, catechin, epicatechin, ellagic acid
Uliana *et al*., 2016. Brazil (ES)	Fresh leaves	Essential oil, ethanol extract	GC/MS, LC–MS/MS	Oil: 32 constituents identified. Main compounds: γ-3-carene, E-caryophyllene, myrcene and α-pinene Extract-major components: ferulic and caffeic acids and quercetin
Feuereisen *et al*., 2017. Germany	Exocarp/drupes	Ethanol and acetic acid extracts	HPLC, UHPLC-DAD-MS/MS	3 anthocyanins (pelargonidin 3-O-galactoside, 7-O-methylcyanidin 3-O-galactoside and 7-O-methylpelargonidin 3-O-galactopyranoside) and 3 biflavonoids (I6,II8-biapigenin (agathisflavone), I30,II8-biapigenin (amentoflavone) and II-2.3-dihydro-I30,II6-biapigenin)
Feuereisen *et al*., 2017. Germany	Fruits	Methanolic extract	UHPLC−DAD−MS/MS	Anthocyanins: cyanidin 3-O-galactoside, pelargonidin 3-O-galactoside, 7-O-methylcyanidin 3-O-derivative, 7-O-methylcyanidin 3-O-galactoside, 7-O-methylcyanidin galloylhexoside. Biflavonoids: I6,II8-biapigenin, II-2.3-dihydro-I3',II8-biapigenin, I3', II8-biapigenin, I3',II6-biapigenin, I4'-O,II6-biapigenin, I,II-2.3-tetrahydro-I3',II8-biapigenin

Carneiro *et al*., 2017. Brazil	Leaves	Hexane extract	GC-MS	Main compounds: α-pinene, limonene, carene, and phellandrene
Martinelli *et al*., 2017. Brazil (MG)	Fruits	Essential oil	GC-MS	α-pinene, α-phellandrene, β-pinene, β-mircene, trans- 3-caren-2-ol, o-cimene and (-)-limonene
Nunes-Neto *et al*., 2017. Brazil (PE)	Stem bark	Ethanolic extract	HPLC	Gallic acid, catechin, epicatechin and ellagic acid
Piras *et al*., 2017. Tunisia	Leaves and ripe fruits	Volatile oil	GC-FID and GC-MS	Main compounds: α-pinene, α-phellandrene, β-phellandrene, germacrene D and bicyclogermacrene
Rocha *et al*., 2017. Brazil (MS)	Leaves	Methanolic extract	Total phenolic compound, flavonoid, tannin and ascorbic acid contents, presence of saponins	Phenolic compounds, flavonoids, tannins and ascorbic acid
Silva *et al*., 2017. Brazil (MS)	Leaves	Methanolic extract	HPLC, 1D and 2D NMR	One steroid, sitosterol-3-O-β-glucopyranoside; two gallic acid derivatives, 1,2,3,4,6-penta-O-galloyl-β-glucopyranoside and methyl gallate; and four flavonoids: robustaflavone, quercetin, quercetrin and luteolin
Ennigrou *et al*., 2018. Tunisia	Leaves and twigs	Essential oil	GC-MS	High amount of monoterpene hydrocarbons. Main compounds: a-phellandrene a-pinene and limonene
Salem *et al*., 2018. Egypt	Ripe fruits	Essential oil, acetone extract, *n*-hexane extract	GC-MS	Oil-major components: α-pinene and α-phellandrene. Acetone extract-major components: oleic acid, α-phellandrene and δ-cadinene. *n*-hexane extract-major methyl esters of fatty acids: oleic and palmitic
Silva *et al*., 2018. Brazil (ES)	Fruits and leaves	Ethanolic extract	(-)-ESI-TOF-MS	Fruits-major compounds: phenolic acids, fatty acids, acid triterpenes and biflavonoids. Leaves-major compounds: phenolic acids, tannins, fatty acids and acid triterpenes
Tlili *et al*., 2018. Tunisia	Mature fruits	Methanolic extract	HPLC	Main compounds: catechin, luteolin and kampferol

1D NMR= One-dimensional nuclear magnetic resonance spectroscopy; 2D NMR= Two-dimensional nuclear magnetic resonance spectroscopy; ESI-TOF-MS= Electrospray Ionization Time-of-Flight Mass Spectrometer; GC= Gas chromatography; GC-FID= Gas chromatography with flame-ionization detection; GC-MS= Gas chromatography with mass spectrometry; HPLC= High-performance liquid chromatography; LC= Liquid chromatography; LC-MS/MS= Liquid chromatography–tandem mass spectrometry; NMR= Nuclear magnetic resonance; UHPLC-DAD= Ultra-high-performance liquid chromatography-diode-array detection; UHPLC-DAD-MS/MS= Ultra-high-performance liquid chromatography-diode-array detection–tandem mass spectrometry.

Table 2 – Antimicrobial activity

Authors, year, Country	Part	Preparation	Microorganisms	Results			Score* (Aligiannis *et al.*, 2001)
				MIC (µg/mL)	Inhibition Zone Diameter (mm)	IC 50	
Antifungical activity							
Martínez *et al*., 2000. Cuba	Leaves	Ethanolic extract	*C. albicans*	---	25.3	---	---
Braga *et al*., 2007. Brazil (MG)	Leaves	Methanol extract	*C. albicans* *C. neoformans*	1250 156	15 20	---	Moderate Strong
Johann *et al*., 2008. Brazil (SC)	Leaves	Ethyl acetate fraction	*C. albicans*	7.8	----	---	Strong
Gundidza *et al*., 2009. South Africa	Fresh leaves	Essential Oil	*C. albicans* *A. flavus* *A. niger* *P. notatum*	---	49.8 36.4 58.1 48.7	---	---
El-Massry *et al*., 2009. USA	Leaves	Dichloromethane extract	*A. niger* *A. parasiticus* *C. albicans*	750 800 700	---	---	Moderate Moderate Moderate
Johann *et al*., 2010. Brazil (SC)	Leaves	Schinol and biphenyl compound isolated	*P. brasiliensis* (Pb18, Pb01, Pb3, PbB339, Pb1578)	7.5 – 125 15.6 – 250	---	---	Strong
Gomes *et al*., 2012. Brazil (PE)	Leaves	Crude extract x SteLL	*C. albicans*	12.75 x 6.5	---	---	Strong
Alves *et al*., 2013. Brazil (PB)	-	Tincture	*C. albicans*	312.5	---	---	Strong

Uliana *et al*., 2016. Brazil (ES)	Leaves	Ethanolic extract	*C. albicans*	75	---	---	Moderate
Torres *et al*., 2016. Brazil	Bark	Aqueous extract	50 strains of the Candida genus from patients of Hospital Santa Casa de Misericórdia (SP) and standard strain of each species: *C. albicans*, *C. krusei*, *C. glabrata* and *C. tropicalis*	---	0	---	---
Martinelli *et al*., 2017. Brazil (MG)	Fruits	Essential oil	*C. albicans* *A. niger* *Penicillium sp*	0.25% - 0.25%	---	---	---
Piras *et al*., 2017. Tunisia	Ripe fruits	Volatile oil	*C. neoformans*	320-640	---	---	Strong-moderate
			Antibacterial activity				
Martínez *et al*., 2000. Cuba	Leaves	Ethanolic extract	*S. aureus* *E. coli* *P. aeruginosa*	---	23.8 23.6 24.3	---	---
El-Massry *et al*., 2009. USA	Leaves	Dichloromethane extract	*S. aureus* *P. aeruginosa*, *E. coli*	600 550 850	---	---	Strong Strong Moderate
Gundidza *et al*., 2009. South Africa	Fresh leaves	Essential oil	*A. calcoaceticus* *B. subtilis* *C. freundii* *C. erfringens* *C. Sporogenes* *E.coli* *K. pneumoniae* *P. vulgaris* *P. aeruginosa* *S. typhii* *S. aureus* *Y. enterocolitica*	---	12.0 10.0 8.0 8.9 9.2 13.2 10.0 7.0 11.2 6.0 8.0 17.0	---	---

Gomes *et al*., 2012. Brazil (PE)	Leaves	SteLL	*E. coli* *K. pneumoniae* *P. aeruginosa* *P. mirabilis* *S. aureus* *S. enteritidis*	28.75 3.59 1.79 3.59 1.79 0.45	---	---	Strong Strong Strong Strong Strong Strong
Bernardes *et al*., 2014. Brazil (RJ)	Fruits peels	Methanol extract, flavonoid fraction	*Mycobacterium bovis* *BCG*	--- 	---	279.5 108.5	---
Cole *et al*., 2014. Brazil (ES)	Ripe fruit	Essential oil	*E. coli* *K. oxytoca* *Pseudomonas sp.* *Enterobacter sp.* *E.agglomerans* *Streptococcus Group D* *S. aureus* *Corynebacterium sp.* *Bacillus sp.* *Nocardia sp.*	28.43 28.43 7.11 56.86 28.43 14.21 14.21 3.55 7.11 7.11	---	---	Strong Strong Strong Strong Strong Strong Strong Strong Strong Strong
Costa *et al*., 2015. Brazil (BA)	Stem and leaves	Ethanol extract	*E. Faecalis*	62.5 15.62	---	---	Strong
Dannenberg *et al*., 2016. Brazil (RS)	Fruit	Essential oil of green fruit x Essential oil of mature fruit	*S. aureus* *L. monocytogenes* *B. cereus* *S. mutans* *C. fim* *S. dysenteriae* *P. aeruginosa* *A. hydrophila*	6799 x 1704 6799 x 6820 850 x 852 3400 x 27278 13598 x 6820 27197 x 6820 6799 x 6820 1700 x 6820	41.23 x 42.70 35.22 x 40.86 31.39 x 39,97 31.20 x 42.62 40.58 x 53.14 35.44 x 38.80 44.31 x 41.33 40.16 x 41.36	---	Weak Weak Moderate Weak Weak Weak Weak Weak

Ennigrou *et al*., 2016. Tunisia	Immature, halfmature and full mature fruits	Essential oil	*E. feacium* *S. agalactiae* *E. coli* *S. typhymurium*	---	Immature 10.5±0.28 20.16±0.72 8.83±0.16 7.5±0.28	Halfmature 14.33±0.44 23.16±0.6 9.5±0.28 8.67±0.16	Mature 19.83±0.44 28.5±0.72 11.17±0.16 10.5±0.28	---	---
Uliana *et al*., 2016. Brazil (ES)	Leaves	Essential oil and ethanolic extract	*S. aureus* *E. coli*	500 250		---		---	Strong Strong
Martinelli *et al*., 2017. Brazil (MG)	Fruits	Essential oil	*E. coli* *S. aureus* *B. cereus*	0.25% 0.50% 0.10%		---		---	---
Ennigrou *et al*., 2018. Tunisia	Leaves and twigs	Essential oil	*E. feacium* *S. agalactiae* *E. coli* *S. typhymurium*	---	Leaves 31.83±1.5 27.5±0.5 10.5±0.5 10±0		Twigs 25.5±0.5 7.67±1.5 7.83±1 8.33±0.5	---	---
Salem *et al*., 2018. Egypt	Ripe fruits	Essential oil	*A. baumannii* *B. subtilis* *E. coli* *M. flavus* *P. aeruginosa* *S. lutea* *S. aureus*	> 2000 250 500 128 32 500 16		0 14.6 ± 0.6 11 ± 1 15.3 ± 0.3 18.3 ± 0.3 13.3 ± 0.8 16.3 ± 0.6		15.11±0.99	Weak Strong Strong Strong Strong Strong Strong
		Acetone extract	*A. baumannii* *B. subtili* *E. coli* *M. flavus* *P. aeruginosa* *S. lutea* *S. aureus*	8 4 16 4 128 128 8		18.3 ± 0.3 14.6 ± 0.6 15.3 ± 0.8 20.3 ± 0.3 18.3 ± 0.3 13.3 ± 0.3 18.3 ± 0.3		118.16±1.7	Strong Strong Strong Strong Strong Strong Strong
		n-hexane extract	*A. baumannii* *B. subtili* *E. coli* *M. flavus* *P. aeruginosa* *S. lutea* *S. aureus*	1000 1000 10000 10000 >2000 >2000 >2000		6.6 ± 0.3 8.6 ± 0.6 10.0 ± 0.6 7.3 ± 0.3 0 10.6 ± 0.6 0		324.26±2.45	Moderate Moderate Moderate Moderate Weak Weak Weak

Silva *et al*., 2018. Brazil (ES)	Fruits and leaves	Ethanolic extract	*E. coli*	78	---	---	Strong
Antiviral activity							
Nocchi *et al*., 2016. Brazil (PR)	Stem bark	Crude hydroethanolic extract	*Herpes simplex virus type 1 (HSV-1)*	---	---	14	---
Antiparasitaric activity							
Morais *et al*., 2014. Brazil (SP)	Leaves	3 natural tirucallane triterpenoids isolated	*L. infantum* (Promastigotes) *L. infantum* (Amastigotes) *T. cruzi*	---	---	57.82 28.95 16.28	---

IC 50= 50% inhibitory concentration; MIC= Minimum inhibitory concentration; SteLL= *S. terebinthifolius* leaf lectin.

*Aligiannis *et al*. (2001) proposed a classification for the antimicrobial activity of plant products, considering strong activity substances with MIC up to 0.5 mg/ml, with moderate antimicrobial MIC values of 0.6–1.5 mg/ml, and weak antimicrobial MIC above 1.6 mg/ml (ALIGIANNIS et al., 2001).

Table 3 – Healing activity

Authors, year, Country	Part	Preparation	Animal	Animals models	Results
Castelo Branco Neto *et al*., 2006, Brazil (MA)	Inner bark	Hydroalcoholic extract (topic)	Rat	Skin open wounds	Delayed the reepitelization of the skin wounds
Coutinho *et al*., 2006, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg i.p.)	Rat	Colonic anastomosis	Favorable effect in the healing process of colonic anastomosis
Lucena *et al*., 2006, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg i.p.)	Rat	Bladder surgical incisions	Favorable effect in the healing process of cystotomies
Nunes Jr *et al*., 2006, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg i.p.)	Rat	Abdominal wall cut	Macroscopic analysis: did not alter healing process. Histological analysis: healing effect
Santos *et al*., 2006, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg i.p.)	Rat	Stomach injury and suture	Extract did not alter the stomach healing process
Santos *et al*., 2012, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg p.o.)	Rat	Stomach injury and suture	Accelerated the stomach healing in rat
Estevão *et al*., 2013, Brazil (PE)	Essential oil, fresh leaves	Ointment	Rat	Skin wound healing	Accelerates the healing process of wounds
Santos *et al*., 2013, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg p.o.)	Rat	Stomach injury and suture	Favored the gastric wound healing in rats
Estevão *et al*., 2015, Brazil (PE)	Essential oil, fresh leaves	Ointment	Rat	Skin wound healing	Increases mast cell concentration and promotes skin wound contraction
Scheibe *et al*., 2016, Brazil (MA)	Inner bark	Hydroalcoholic extract (100mg/kg p.o.)	Rat	Cecotomy and cecorrhaphy	Favored the healing process

Estevão *et al*., 2017. Brazil (PE)	Essential oil, leaves	Ointment	Rat	Skin wound healing	Increases the number of blood vessels and collagen fibers deposition

i.p.= Intraperitoneal; p.o.= Oral.

Table 4 – Anti-inflammatory activity

Authors, year, Country	Part	Preparation	Mainly compounds	Models	Assays	Results
			In Vitro			
Bernardes *et al*., 2014, Brazil (RJ)	Fruit peels	Methanolic extract (exhaustive extraction), fraction A3 and apigenin isolated	Apigenin	*In vitro*	DPPH	Results suggest that the flavonoids are responsible for the inhibition of NO production by macrophages and for the ability to scavenge free radicals
			Animals			
Formagio *et al*., 2011, Brazil (MS)	Fruits	Essential oil	Monoterpenes	Rat Edema: dose dependent AP: 100mg/kg p.o. CFA: 200mg/kg p.o.	Carrageenan-induced rat paw edema and leukocyte migration in the AP model and inflammation induced by CFA	The essential oil exhibited a marked anti-inflammatory activity
Fedel-Miyasato *et al*., 2014, Brazil (MS)	Leaves	Methanolic extract	Caffeic and p-coumaric acids, quercetin, luteolin and apigenin	Mice Edema: 0.1, 0.3 and 1mg/ear AP: 100mg/kg p.o	Croton oil-induced ear edema AP	The topical application of extract in induced edema and in the air pocket model inhibited leukocyte migration and plasma leakage
Rosas *et al.*, 2015, Brazil (RJ)	Leaves	Hydroalcoholic extract	Gallic acid, methyl gallate and pentagalloylglucose.	Male Swiss and C57Bl/ 6 mice (100mg/kg p.o)	Zymosan-induced arthritis	The extract inhibited leukocyte (primarily neutrophils) migration, cytokine and chemokine production in inflammatory models
Estevão *et al*., 2017. Brazil (PE)	Essential oil, leaves	Ointment containing 10% leaf oil	-	Rat	Skin wound	A significant reduction in TNF-α, CXCL-1 and CCL-2 levels was observed. Essential oil reduced neutrophil and macrophage in the local
Nunes-Neto *et al*., 2017. Brazil (PE)	Stem bark	Ethanolic extract	Gallic acid, catechin, epicatechin and ellagic acid	Rat (100, 200, and 400 mg/kg p.o)	Paw edema induced by histamine	The extract caused a dose-dependent decrease of edema, and high dose exhibited equivalent effects to hydroxyzine

Silva *et al*., 2017. Brazil (MS)	Leaves	Methanolic extract	One steroid, sitosterol-3-O-β-glucopyranoside; two gallic acid derivatives, 1,2,3,4,6-penta-O-galloyl-β-glucopyranoside and methyl gallate; and four flavonoids: robustaflavone, quercetin, quercetrin and luteolin	Male Swiss mice (Extract or fraction – 100 and 300 mg/kg p.o and fraction intraplantarly - 10 and 100 mg/kg)	Carrageenan-induced paw oedema	Extract and fraction treatments inhibited oedema formation but did not alter the increase in MPO activity induced by carrageenan
Human						
Freires *et al*., 2013, Brazil (PB)	Stem bark	Tincture (0.3125%) - mouthwashes	---	Human (children with gingivitis)	Gingival inflammation levels and biofilm accumulation	Mouthwashes showed significant anti-inflammatory activity (equivalent to CHX), but it was not able to reduce biofilm accumulation
Lins *et al*., 2013, Brazil (PB)	---	Hydroalcoholic extract - mouthwashes	---	Human (> 18 years old)	Patients with chronic gingivitis	Reduction of gingival inflammation

AP= Air pouch; CFA= Complete Freund's adjuvant; CHX= Chlorhexidine; DPPH= 2,2-diphenyl-1-picrylhydrazyl radical; NO= Nitric oxide; p.o.= Oral.

Table 5 – Antioxidant activity

Authors, year, Country	Mainly compounds	Part	Preparation	Assays	Results
			In vitro		
Ceruks *et al*., 2007, Brazil (SP)	Ethyl gallate, methyl gallate, quercitrin, myricetrin and myricetin	Leaves	Ethanolic extract	DPPH	Results suggest that the isolated substances are responsible for the antioxidant activity found
El-Massry *et al.*, 2009, Egypt and USA	EO: terpenes (cis-β-terpineol, (E)-caryophyllene, β-cedrene and citronellal) EE: caffeic, coumaric and syringic acids	Leaves	Essential oil, dichloromethane extract and ethanolic extract	DPPH and β-carotene/bleaching assays	All samples exhibited antioxidant activity with dose response. Ethanolic extract presented higher concentration of phenolic contents (comparable to that of butyl hydroquinone) > Essential oil > Dichloromethane extract
Bendaoud *et al*., 2010, Tunisia and France	Monoterpenes: α- and β-phellandrene	Riped berries	Essential oil	DPPH and ABTS	ABTS IC 50 24 ± 0.8 mg/L > activity antioxidant DPPH IC 50 > 10000. Relationships between chemical composition and biological activities
Bernardes *et al*., 2014, Brazil (RJ)	Apigenin	Fruit peels	Methanol extract (exhaustive extraction), fraction A3 and apigenin isolated	DPPH	Ability to eliminate free radicals. The results suggest a relation with the flavonoids present
Costa *et al*., 2015, Brazil (BA)	---	Fruits, stem, stem bark and leaves	Ethanolic extract	DPPH	All samples tested showed antioxidant activity. The comparison between extracts suggests that the activity is increased for samples obtained with Soxhlet
Ennigrou *et al*., 2016. Tunisia	EO: α-phellandrene, α-pinene and limonene. ME: highest total phenol contents in full mature fruits and highest total flavonoid contents in halfmature fruits	Immature, halfmature and full mature fruits	Essential oil and methanolic extract	DPPH	The extract presented greater radical scavenging activity than the essential oil

Uliana *et al*., 2016, Brazil (ES)	EO: γ-3-carene, E-caryophyllene, myrcene and α-pinene. EE: ferulic and caffeic acids, and quercetin	Leaves	Essential oil and ethanolic extract (maceration and ultrasound)	DPPH	Relationship between the antioxidant activity and the total phenolic content (r = 0.98). Maceration > ultrasound
Silva *et al*., 2017. Brazil (MS)	One steroid, sitosterol-3-O-β-glucopyranoside; two gallic acid derivatives, 1,2,3,4,6-penta-O-galloyl-β-glucopyranoside and methyl gallate; and four flavonoids: robustaflavone, quercetin, quercetrin and luteolin	Leaves	Methanolic extract and isolated compounds (sitosterol-3-O-β-glucopyranoside, 1,2,3,4,6-penta-O-galloyl-β-glucopyranoside, methyl gallate, robustaflavone, quercetin, quercetrin and luteolin)	DPPH, β-Carotene/linoleic acid assay, ABTS	Methanolic extract presented potent antioxidant activity attributed to various compounds found, and isolated compounds, except robustaflavone, were active in all assays
Ennigrou *et al*., 2018. Tunisia	High amount of monoterpene hydrocarbons. Main compounds: a-phellandrene a-pinene and limonene	Leaves and twigs	Essential oil	DPPH	Low DPPH radical scavenging activity
Salem *et al*., 2018. Egypt	EO: *α*-pinene and *α*-phellandrene. ACE: oleic acid, *α*-phellandrene and *δ*-cadinene. HexE: oleic and palmitic acids.	Ripe fruits	Essential oil, acetone extract and *n*-hexane extract	DPPH	Promising antioxidant activity of EO and ACE (IC 50 EO 15.11±0.99, ACE 118.16±1.7, HexE 324.26±2.45 μg/mL)
Scheid *et al*., 2018. Brazil (RS)	All fractions: anthraquinones and triterpenes/steroids. Ethyl acetate and methanol fraction:	Leaves	n-hexane, dichloromethane, ethyl acetate and metanol fractions	DPPH, Hydroxyl Radical Scavenging Activity, TRAP	DPPH: metanol and ethyl acetate fractions showed excelent scavenging activities. Hydroxyl scavenging assay: dichloromethane and methanol fractions showed higher values. TRAP: greatest potential found in the metanol fraction

	flavonoids and saponins. Methanol fraction: coumarins.				
Tlili *et al*., 2018. Tunisia	Catechin, luteolin and kampferol	Mature fruits	Methanolic extract	TAC, DPPH	Ability to eliminate free radicals due to its total phenolics, flavonoids and tannins contents
			Cells		
Rocha *et al*., 2017. Brazil (MS)	Phenolic compounds, flavonoids, tannins and ascorbic acid	Leaves	Methanolic extract	DPPH, SOD, CAT and GPx activities, Oxidative Hemolysis and Lipid Peroxidation Doxorubicin-Induced ex vivo	The extract possesses beneficial properties reducing doxorubicin-induced oxidative stress in human erythrocytes, probably via antioxidant effects by inhibiting free radicals, decreased oxidative stress (MDA) and increased antioxidant enzyme activity (SOD and GPx)
			Animal		
Sereniki *et al*., 2016, Brazil (PE)	Gallic acid, catechin, epicatechin and ellagic acid	Stem bark	Ethanolic extract	DPPH and lipid peroxidation	Significant DPPH activity (IC 50 12.176 ± 0.077µg/mL) and pre-treatment at all doses inhibited lipid peroxidation, suggesting a neuroprotective effect mediated by its antioxidant activity

ABTS= 2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) radical; ACE= Acetone extract; CAT= catalase; DPPH= 2,2-diphenyl-1-picrylhydrazyl radical; EE= Ethanolic extract; EO= Essential oil; GPx= glutathione peroxidase; HexE= *n*-hexane extract; IC 50= 50% inhibitory concentration; ME= Methanolic extract; *SOD*= superoxide dismutase; TAC= total antioxidant capacity; TRAP= Total Reactive Antioxidant Potential.

Figure captions

Figure 1 – *Schinus terebinthifolius* Raddi.

Source: own author.

Figure 2 – Search and selection results.

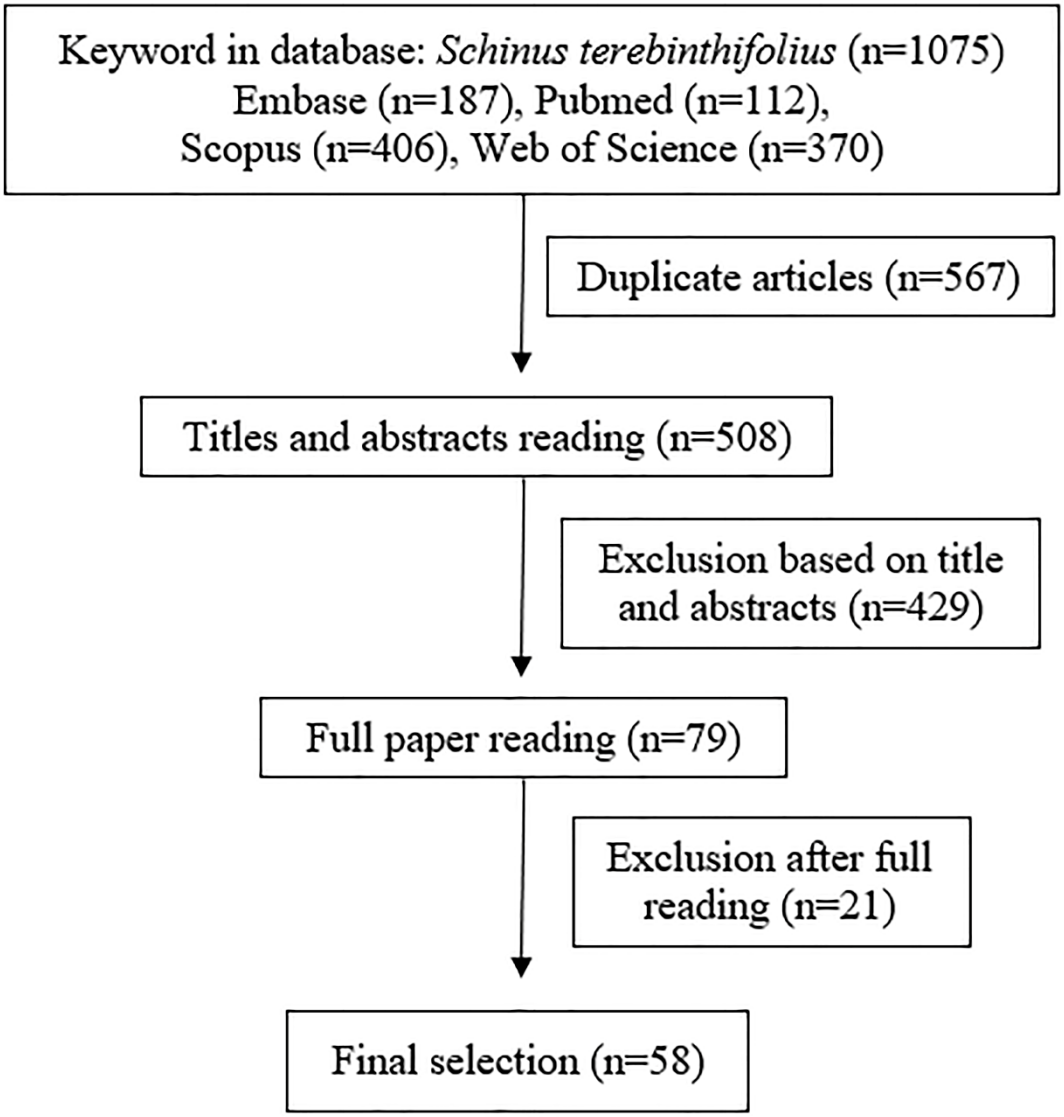
Source: own author.

Figure 3 – Some major phenolic compounds of the species *Schinus terebinthifolius*: a- ethyl gallate; b- myricetin; c- methyl gallate; d- caffeic acid; e- p-coumaric acid; f- ellagic acid; g- gallic acid; h- catechin.

Source: *ChemDraw*® Software.

Figure 4 – Some major compounds from essential oil from different parts of the species *Schinus terebinthifolius*: a-β-caryophyllene; b-α-pinene; c-germacrene D; d-β-pinene; e-α-fenchene; f-β-myrcene; g-α-phellandrene; h-limonene; i-isosylvestrene; j-γ-cadinene.

Source: *ChemDraw*® Software.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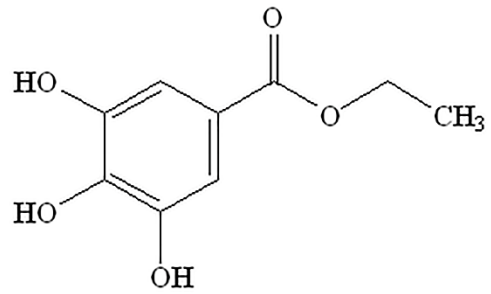
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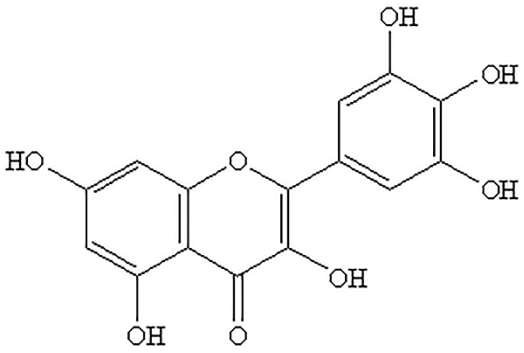
HO
O
CH3
HO
OH

b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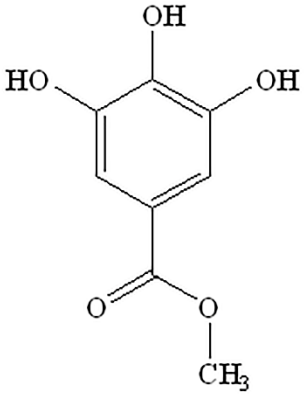
HO
O
OH
OH
OH
O

c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O
O
CH3

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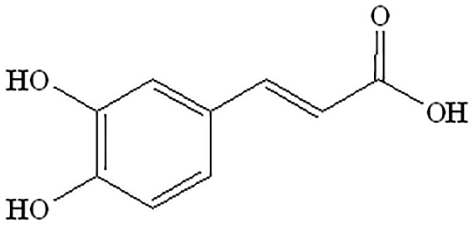
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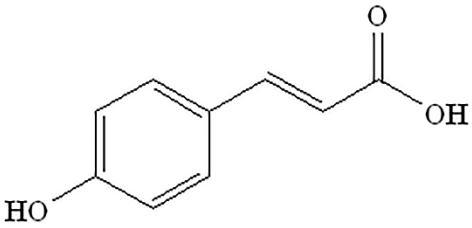
OH
HO

e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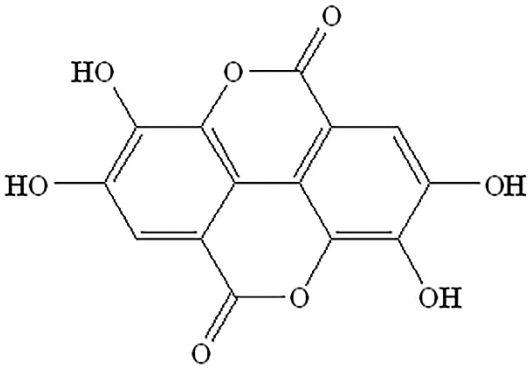
f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HO
OH
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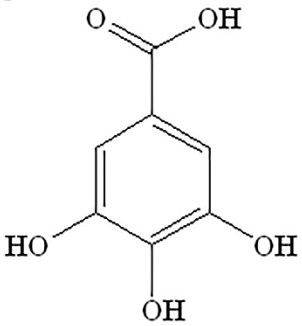
OH
O

g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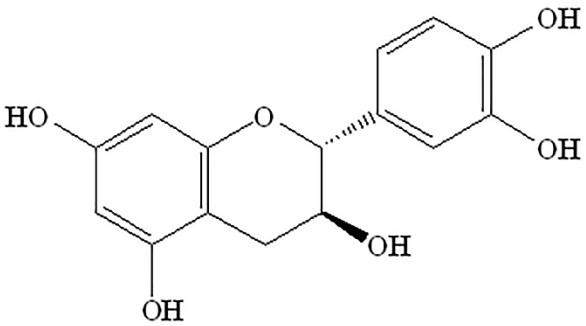
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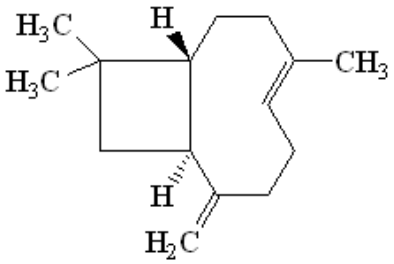
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H
H2C

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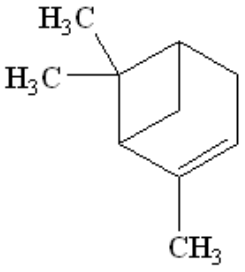
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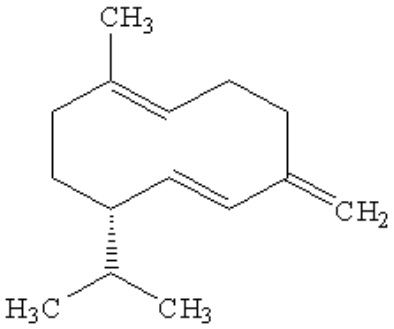
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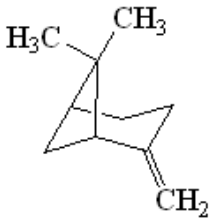
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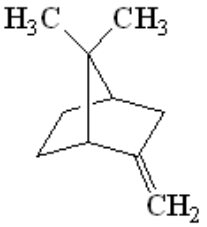
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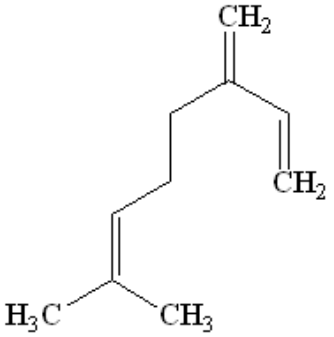
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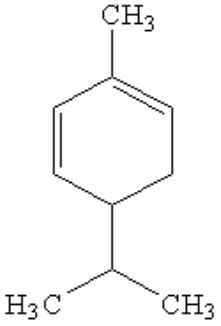
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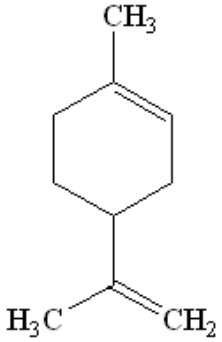
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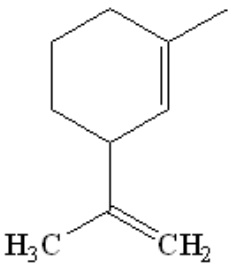
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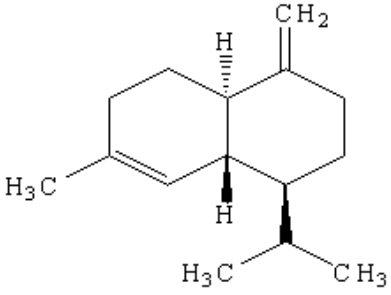
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H
H3C
H
H3C
CH3

ARTIGO II

Pink pepper (*Schinus terebinthifolius* Raddi): compounds present on fruits and its antioxidant and anti-inflammatory activities.

(Artigo nas normas da revista Phytotherapy Research)

Pink pepper (*Schinus terebinthifolius* Raddi): compounds present on fruits and its antioxidant and anti-inflammatory activities

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Abstract

Schinus terebinthifolius Raddi, popularly known as pink pepper, is commonly used for medicinal purposes and presents great economic and gastronomic potential. Consumption of spices can reduce the risk of chronic diseases due to its antioxidant and anti-inflammatory properties. The objective was to identify and quantify compounds present in extracts and in essential oil of *S. terebinthifolius* fruits and to evaluate its antioxidant and anti-inflammatory capacities. Results indicated free radical capture in both extracts, and the ethanolic extract showed better capture activity of ABTS radical. Reduction potential, with emphasis on the aqueous extract, and protection against lipid oxidation of both extracts were observed. This activity may be associated with the content of gallic and caffeic acids and the flavonoids naringenin and quercetin. While in the essential oil, γ-3-carene, α-felandren, β-felandren, α-pinene and elemol represent more than 80% of the compounds found and antioxidant activity was observed by the capture of free radicals and by reduction potential. The ethanolic extract decreased ear edema by reduction of myeloperoxidase activity. Thus, present compounds indicate that this pepper can have important biological activity and should be better explored, reinforcing the role that spices have in cooking and its possible health benefits.

Keywords: Anacardiaceae. Antioxidants. Inflammation.

1 INTRODUCTION

Schinus terebinthifolius Raddi, popularly known as Brazilian pepper or pink pepper, belongs to the family Anacardiaceae, which has many edible fruits with distinct characteristics. This species is native from South America and its fruits are highly appreciated as a spice around the world (Álvares-Carvalho et al., 2016; Carneiro et al., 2017).

Different plant parts such as fruits, seeds, leaves and stem bark are commonly used for medicinal purposes and confer to *S. terebinthifolius* health benefits due to pharmacological properties such as anti-inflammatory, anticancer, antiulcerogenic, antioxidant, antimicrobial and healing activities (Santos, Silva, & Caxito, 2015).

S. terebinthifolius contains various phenolic compounds such as flavonoids, ethyl gallate, quercitrin, myristylrine, myricetin, methyl gallate, caffeic acid, siringeic acid, coumaric acid, ellagic acid, gallic acid and catechin (Feuereisen et al., 2014, 2017; Sereniki et al., 2016; Uliana et al., 2016).

These bioactive compounds, derived from the secondary metabolism of plants present in spices, play an important role in reducing the adverse effects caused by oxidative stress and inflammation, often present in diseases such as diabetes, hypertension, obesity, atherosclerosis, Parkinson's disease, Alzheimer's and cancer (Francisqueti et al., 2017; Halliwell & Grootveld, 1987).

Thus, the habitual consumption of a diet rich in spices may contribute to the reduction of the risk of these diseases by the improvement of markers of oxidative stress and decrease damage to the DNA (Mitjavila et al., 2013), since the antioxidants present are able to combat oxidative stress and inflammation and, consequently, its deleterious effects to the organism (Francisqueti et al., 2017).

Knowledge about the composition and potential biological effects of *S. terebinthifolius* fruits should be further explored in studies, since they play an important economic and gastronomic potential for the population, besides, new researches may contribute to a better understanding of the species and utilization by the food industry. In addition, the search for bioactive compounds that may delay or suppress oxidative stress and consequently regulate the redox state of tissues, in addition to attenuating inflammation, has a fundamental importance in nowadays due to the high prevalence of chronic non-communicable diseases and their outcomes for population health. Thus, the present work intends to identify and quantify the compounds present in *S. terebinthifolius* fruits, in addition to evaluating its antioxidant and anti-inflammatory properties.

2 MATERIALS AND METHODS

2.1 Botanical material: collection and extraction

Fresh fruits of *S. terebinthifolius* were collected by Prof. Dr. Marcelo Cavalcante Duarte, in September 2016 at Aracaju, Sergipe, Brazil (10º57'45.6"S, 37º02'39.5"W), and identified by the biologist Marta C. V. Farias, Department of Biology/Federal University of Sergipe (UFS). Specimens were deposited in the UFS Herbarium (ASE 39745). Authorization of access to genetic resources: SisGen – A006910. The fruits were prepared by leaving them in the shade at room temperature until dry, only mature fruits with no visible signals of damage were collected. The fruit was ground and 5 g were mixed with 50 ml of distilled water or ethanol and placed under magnetic stirring for 24 hours. Subsequently, it was centrifuged for 15 minutes and the supernatant contents were vacuum filtered, the aqueous extract of *S. terebinthifolius* (AEST) was lyophilized and the ethanolic extract of *S. terebinthifolius* (EEST) was rotaevaporated. All extracts were kept in well-closed amber glass vials under refrigeration until used for phytochemical and antioxidant screening. To obtain the

essential oil of *S. terebinthifolius* (EOST), 100 g of fruits were immediately ground in an analytical mill (model IKA A11 basic, Wilmington, USA) before the process of obtaining the oil by hydrodistillation using a Clevenger type, temperature controlled system, less than 100 °C for 2 hours, using a proportion of 2 L of water per 100 g of plant material. After extraction, the oil / water mixture was collected, dried with anhydrous sodium sulfate (Na_2SO_4), filtered and stored under refrigeration until tests were carried out.

2.2 Quantification of phenolic and flavonoids content and characterization of phenolic compounds in extracts

Total phenolic content was analyzed by the method of Folin-Ciocalteau (Swain & Hillis, 1959) with some modifications. The absorbance was measured at 720 nm and the results were expressed in gallic acid equivalents (GAE), determined by a curve (12.5 to 200 μg / mL). The total flavonoids were determined by the method of Zhishen, Mengcheng and Jianming (1999), with some modifications using the aluminum trichloride ($AlCl_3$) method. Catechin was used to calculate the standard curve (0.125 to 2 μg), the absorbance was measured at 510 nm and the results were expressed as catechin equivalents.

The AEST and EEST fruits were diluted with 2 mg / mL ultrapure methanol / water (50:50 v / v) (50 mg of each extract in 25 mL of methanol / water).

Chromatographic profile analysis was performed using a high performance liquid chromatography system consisting of a DGU-20A3 degenerator, two LC-20AD pumps, a SIL-20A HT auto injector, a CTO-20A column oven, a detector SPDM20Avp photodiode array (DAD) and a CBM-20A system controller (Shimadzu Co., Kyoto, Japan). Chromatographic separation was performed using the Phenomenex Luna® C18 analytical column 4.6 x 250 mm (particle size 5 μm) and a 30 x 4 mm Phenomenex C18 protection cartridge system (4 μm particle size). The solvents used for the mobile phase were: (A) 0.5% acetic acid in water and

(B) methanol which were degassed using an ultrasonic bath. The injection volume of the sample was 20 μL and the flow rate of the mobile phase was 1.0 mL / min. The elution gradient started with 5% B for 3 minutes, 5-10% B for 3-10 minutes, 10-45% B for 10-15 minutes, 45-55% B for 15-20 minutes, 55-63% B for 20-25 minutes, 63-70% B for 25-30 minutes, 70-100% B for 30-33 minutes, 100-5% B for 33-40 minutes, returning the initial conditions and terminating the analysis. The oven temperature was 25 ° C and the detector was set at 280 nm to acquire the chromatograms.

The compounds present in the samples were identified by co-injections of standards comparing retention times and ultraviolet absorption spectra. Caffeic acid, gallic acid, naringenin, and quercetin were obtained from Sigma-Aldrich® and diluted with 500 μg/mL methanol (stock solution). Quantitative analyzes were performed by preparing calibration curves for each standard at concentrations: 1, 25, 50, 75 and 100 μg/mL. Each point of the curve was filtered with membrane filters (PTFE - 0.45 μm) prior to HPLC injection and analyzed in triplicate.

2.3 Identification and quantification of the compounds present in essential oil

Chemical analysis of the EOST were performed as described in Santos et al. (2015). Gas chromatography/mass spectrometry/flame ionization detector (CG/MS/FID) analyzes were performed using GC / MS / FID (GCMSQP2010 Ultra, Shimadzu Corporation, Kyoto, Japan) equipped with an AOC automatic injection sampler -20i (Shimadzu). Separations were performed on a Rtx®-5MS Restek (5% -diphenyl-95% -dimethylpolysiloxane) silica capillary column 30 mx 0.25 mm internal diameter, 0.25 μm film thickness, in a constant flow of Helium 5.0 with a rate of 1.0 mL min-1.

2.4 *In vitro* antioxidant capacity of *S. terebinthifolius* fruits

The *in vitro* experiments described below were performed in triplicate and Trolox (100 or 1000 μg/mL) was used as a positive control. For the analysis of the AEST and EEST, a stock solution of 2000 μg/mL was prepared, and then diluted in different concentrations (100, 50, 1000 and 2000 μg/mL) and the EOST was also diluted (30, 100 and 300 μg/mL).

The antioxidant capacity against the 2,2-Diphenyl-1-picrylhydrazyl radical (DPPH) was evaluated as described by Brand-Willians, Cuvelier and Brest (1995) with minor modifications. The absorbance was read at 515 nm and its values were expressed as percentage of DPPH: % of DPPH = $[(Abs_{control} - Abs_{sample}) / Abs_{control}] \times 100)$.

The radical scavenging capacity of the extract was determined by the ABTS assay, according to the method described by Re *et al*. (1999) with slight modifications. The absorbance was read after 15 minutes at 734 nm and its values were expressed as percentage of ABTS: % of ABTS = $[(Abs_{control} - Abs_{sample}) / Abs_{control}] \times 100)$.

The nitric oxide (NO) scavenging was measured according to the method of Basu and Hazra (2006). The absorbance was measured at 540 nm after 5 to 15 minutes, a standard curve for sodium nitrite ($NaNO_2$) was plotted and the results were expressed as μM of nitrite formed.

The methodology described by Singhal, Paul and Singh (2014) was used for the determination of reducing potential of the extracts and oil, with some modifications. The microplate was incubated at 37ºC in the dark for 30 minutes and read at 595 nm. A standard curve for ferrous sulphate ($FeSO_4$) was generated and the linear equation was used to calculate the reducing power of the extracts.

The methodology described by Miller (1971) using the β-carotene-linoleic acid method was used for the determination of antioxidant activity of the extracts, with some modifications. The emulsion system was incubated for 2 hours at 50 °C and the absorbance was measured at 470 nm. The decay of the optical density of the control ($Abs_{initial}$ - Abs_{final}) was considered as

100% oxidation. The results were expressed as percentage of oxidation protection: % oxidation protection = 100 - [(Abs_{sample} x 100) / $Abs_{control}$].

Evaluation of antioxidant capacity of extracts by inhibition of lipid peroxidation was determined according to Ohkawa, Ohishi and Yagi (1979) with modifications. The experimental protocol using laboratory animals was previously evaluated and approved by the Ethics Committee for Animal Use in Research at UFS (48/2017).

The absorbance was measured at 532 nm, a standard curve for tetraepoxypropane (TEP) was generated and the linear equation was used to calculate the inhibition of lipid peroxidation. The results were expressed in μM of TEP equivalents formed.

2.5 Mouse ear edema induced by TPA

Female mice (20 – 30 g) were obtained from the Animal Center of UFS. Animals were kept at 21-23 ºC with free access to food and water under a 12 hour light/dark cycle. All experiments were conducted in agreement with the guidelines of the Brazilian College of Animal Experimentation and the National Institutes of Health Guidelines and were approved by the Ethics Committee for Animal Use in Research at UFS (48/2017). At the end of the experiments, animals were euthanized by cervical dislocation preceded by excess of inhalatory isoflurane.

Animals (n=36) were divided into groups and 20μL of 12-0-tetradecanoylphorbol-13-acetate (TPA) (1 μg/ear dissolved in acetone) (n=6), acetone (n=8), EEST 1 mg/ear (n=7) and 3 mg/ear (n=7) and dexamethasone (n=8) were applied to the inner and outer surfaces of their ears with a polypropylene tip. After 6 h, the animals were euthanized and its ears were collected. The edema was calculated by the weight of the ears and these tissue samples were submitted to measurement of myeloperoxidase (MPO) activity, FRAP, catalase and superoxide dismutase (SOD) enzymes.

The activity of MPO was determined in ear homogenates prepared in potassium phosphate buffer (50mmol/L, pH 6.0 containing 0.5% hexadecyltrimethylammonium bromide). Aliquots of the homogenates were centrifuged (2 min, 800 g, 4 ºC) and aliquots of the supernatants were incubated with a solution o-dianisidine hydrochloride (0.167 mg/mL containing 0.005% H_2O_2). The activity of MPO was measured as previously described by Bradley, Priebat, Christensen, & Rothstein (1982). Enzyme activity was measured at 460 nm over a period of 5 min. Results were expressed as units of MPO per mg of protein. A unit of MPO was considered as the amount of enzyme that degrades 1 mmol of hydrogen peroxide/min.

FRAP was determined in ear homogenates by the method described above (Ohkawa et al., 1979).

The activity of cytoplasmic SOD was evaluated according to the methodology proposed by McCord and Fridovich (1969), which verifies the production of superoxide anion produced by xanthine oxidase in the presence of xanthine. The determination was made in duplicate and the results were expressed as U / mg protein. A unit (U) was considered, the activity of the enzyme that promoted 50% inhibition of reduction of cytochrome C.

CAT provides the oxidation of hydrogen peroxide (H_2O_2) to H_2O and O_2. The applied methodology was described by Beutler (1975), quantifying the rate of decomposition of H_2O_2. A catalase unit (U) corresponded to the activity of the enzyme that allowed the hydrolysis of 1 μmol H_2O_2.

The protein content of tissues was determined by the Bradford (1985) method using the Bio-Rad® protein assay reagent.

2.6 Statistical analysis

For the statistical treatment of the data, one-way variance analysis (ANOVA) was used, followed by the Tukey test, using Prism® 6.0 software (GraphPad). Data were expressed as mean ± SEM, adopting significance level of $p < 0.05$.

3 RESULTS AND DISCUSSION

3.1 Quantification of phenolic and flavonoids content and characterization of phenolic compounds in extracts

The yield and content values of phenolic compounds and flavonoids of the AEST and EEST are shown in Table 1.

In the AEST and EEST were identified gallic acid, caffeic acid, naringenin and quercetin (Figure 1). Interfering substances are not observed in the retention time of each compound and the UV spectrum of the compound in the extracts were similar to the standard. For the quantification analysis, all the calibration curves prepared for each standard obtained the regression coefficient (r) ≥ 0.999 (linear range 1 - 100 $\mu g.mL^{-1}$). The content of compounds in the AEST and EEST is described in Table 2.

In literature, few studies with the analysis of fruit compounds of *S. terebinthifolius* extracts were performed. A study carried out with the methanolic extract of fruit peels showed three main peaks with the typical UV spectrum of flavonoids, and among them, apigenin was identified. (Bernardes et al., 2014). Another study that aimed to characterize the phenolic composition of *S. terebinthifolius* found four anthocyanins, three biflavonoids, gallic acid and two types of hydrolysable tannins in exocarp extract (Feuereisen et al., 2014).

Feuereisen *et al*. (2017) detected three anthocyanins (pelargonidin 3-O-galactoside, 7-O-methylcyanidin 3-O-galactoside, and 7-O-methylpelargonidin 3-O-galactopyranoside) and three biflavonoids (I6,II8-biapigenin [agathisflavone], I3',II8-biapigenin [amentoflavone], and II-2.3-dihydro-I3',II6-biapigenin) in exocarp extract and a biflavonoid (I3', II8- binarigenin) in

the drupe extract obtained by pressurized liquid extraction. And in the current study distinct flavonoids were identified, among them quercetin and narigenin.

3.2 Identification and quantification of the compounds present in essential oil

A total of 13 compounds were identified, including monoterpenes and sesquiterpenes, and γ-3-carene, α-felandren, β-felandren, α-pinene and elemol represented more than 80% of the EOST composition (Table 3).

In other studies where the analysis of essential oil of fruits was also performed, the authors identified 57, 22 and 17 compounds, being the major components similar to those found in the current study and α-felandren the major compound found in all analyzes in the different percentages of 46.52% (Bendaoud et al., 2010), 14.94% (Affonso et al., 2012) and 12.60% (Cole et al., 2014).

Bendaoud *et al*. (2010) and Cole *et al*. (2014) also identified the α-pinene compound as the major component in their analysis, in 4.34% and 12.59% of the essential oil composition, respectively. In addition, other major compounds found in agreement with the current work were β-felandren (20.81%) (Bendaoud et al., 2010) and γ-3-carene (30.37%) (Cole et al., 2014).

It is noticed that there is great variation between the compounds and their quantities identified in each analysis and it is worth mentioning that most studies find the monoterpenes and sesquiterpenes as volatile compounds present in the essential oil and phenolic acids and flavonoids in extracts. In addition, there may be variations in the concentration of the components found, depending on the region (relative humidity, temperature, altitude, etc.), time of fruit harvest and other factors (Dourado, 2012; Ribeiro, 2015).

3.3 *In vitro* antioxidant capacity of *S. terebinthifolius* fruits

This is the first study that shows the different *in vitro* antioxidant mechanisms of the extracts and the essential oil of the fruits, including the antiradicalar ability, interaction with transition metals, especially Fe, and inhibition of oxidation of lipid substrates.

All concentrations of both extracts significantly decreased the DPPH radical when compared to the system, and they inhibited between 15% and 70% of the radical (Figure 2A) ($p < 0.05$). As well as the extracts, the EOST also significantly decreased the DPPH radical when compared to the system, inhibiting approximately between 24% and 55% of the DPPH radical (Figure 3A) ($p < 0.05$).

In a study carried out with *S. terebinthifolius* leaves, Uliana *et al*. (2016) suggested that phenolic compounds (ferulic and caffeic acids, and quercetin) have a relationship with the antioxidant potential of the extracts. It is worth noting that quercetin and caffeic acid were also identified in the extracts of the current study, and can be related to the antioxidant activity found.

Salem *et al*. (2018) investigated the antioxidant activity of essential oil fruits by the DPPH assay and found a promising antioxidant activity, in addition, the major compounds found were α-pinene and α-felandren, which were also found as some of the major compounds in the current study.

The highest dose of the AEST inhibited 32% and the EEST inhibited between 53% and 83% of the ABTS radical. Comparing the different extracts, it was observed that the EEST inhibited approximately twice the radical at the concentration of 1000 μg/mL and the triple at the concentration of 2000 μg/mL (Figure 2B) ($p <0.05$), probably because the compounds obtained in this type of extraction are more prominent in the ABTS radical inhibition. In relation to the EOST, it inhibited approximately between 35% and 83% of the ABTS radical (Figure 3B) ($p <0.05$).

Silva *et al*. (2017) showed that the methanolic extract of *S. terebinthifolius* leaves presented potent antioxidant activity, by the ABTS assay, attributed to the compounds found, such as quercetin, also found in the current study.

A study by Bendaoud *et al*. (2010) analyzed the antioxidant activity of the essential oil of *S. terebinthifolius* fruits by means of the anti-radical ABTS assay, which showed higher antioxidant activity compared to the DPPH assay, and the authors suggest a relationship between the chemical composition and the biological activities of the plant. It is worth noting that the mainly compounds found were α- and β-phellandrene, which are also the majority in the current research.

The AEST and EEST presented significant NO scavenging activity and produced nitrite in similar amounts (Figure 2C) ($p < 0.05$). These results indicate that the compounds present in the extracts can interact with the NO formed from the SNP decomposition, and thus, protect biological systems from damage caused by NO. Associated with that, Bernardes et al. (2014) demonstrated that extract and fruit peels fractions of *S. terebinthifolius* appear to have an effect under inflammation from the control of nitric oxide production in macrophage culture.

Both extracts and EOST showed a reductive capacity, however the AEST presented greater prominence in the ferric ion conversion (Figures 2D and 3C) ($p < 0.05$). Metal ions such as iron in its ferric form (Fe^{3+}) may react with O^{2-} during the process of oxidative stress forming the ferrous ion (Fe^{2+}), such ion has the ability to interact in the Fenton reaction, producing the hydroxyl free radicals, highly reactive and harmful to the body (Shahidi & Zhong, 2015). Food sources of bioactive compounds, such as phenolic compounds, can act as natural antioxidants, blocking the pro-oxidant effect of Fe^{2+} (Protti et al., 2017). Although it has a reducing ability, the compounds present in the evaluated extracts and essential oil do not act as metal chelators by the ferrozine method (data not shown).

In addition to the mechanisms described above, the extracts inhibited the co-oxidation of β-carotene/linoleic acid system (Figure 2E) ($p < 0.05$). The methanolic extract of *S. terebinthifolius* leaves, when tested in this assay, presented potent antioxidant activity related to the presence of quercetin (Silva et al., 2017).

In the analysis of spontaneous lipid peroxidation, both extracts showed significant antioxidant activity, however, it is noteworthy that in this assay the AEST (37.2 µM of TEP) and EEST (31.5 µM of TEP) performance did not differ from the Trolox standard (100 µg/mL) (36 µM of TEP) (Figure 2F) ($p < 0.05$), differently from other tests where Trolox presented a superior antioxidant activity ($p < 0.05$). In the results of the lipid peroxidation induced by ferric chloride, AEST (62.2 µM of TEP) and EEST (51.1 µM of TEP) presented significant antioxidant activity against lipid peroxidation and exhibited similar performance (Figure 2G) ($p < 0.05$).

Lipid peroxidation occurs initially due to the reaction of a free radical with an unsaturated fatty acid under conditions favorable to oxidation such as time, temperature and oxygen, and subsequent oxidation reactions, resulting in the formation of oxidation end products, such as malondialdehyde, which can be detected in biological samples and used to evaluate oxidative stress (Barrera et al., 2018).

The methanolic extract of *S. terebinthifolius* leaves inhibited lipid peroxidation induced by 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH) probably via antioxidant effects, such as the decrease in malondialdehyde levels and it was found phenolic compounds and flavonoids on its composition (Rocha et al., 2017).

AEST and EEST fruits presented antioxidant activity by the inhibition of spontaneous and induced lipid oxidation, probably due to its content of phenolic antioxidant compounds. And these results corroborate with the obtained in the co-oxidation test of β-carotene/linoleic acid.

It is important to emphasize that the EOST had lower antioxidant activity than the extracts, its analyzes had to be performed at a concentration 15 times greater than the extracts, so not all antioxidant tests were performed. This is due to the EOST composition, since the compounds found (γ-3-carene, α-felandren, β-felandren, α-pinene and elemol) do not present functional groups associated with the antioxidant activity.

As an example, the α-pinene did not present antioxidant activity in the studied conditions (data not shown), but this terpene can exhibit such activity by acting in synergy with other components of the essential oil matrix (Dourado, 2012).

3.4 Mouse ear edema induced by TPA

From the evaluation of the antioxidant capacity by different methods of the AEST and EEST and the EOST of the pepper fruits, one can choose which one had the best results of antioxidant activity and then apply it in the investigation of the antioxidant and anti-inflammatory activities *in vivo*. Thus, the EEST was used to determine these activities. In addition, this extract presented higher content of phenolics and total flavonoids.

The EEST and the group treated with dexamethasone exhibited a significant reduction of the edema (ears weight of 4 and 1.6 mg, respectively) when compared to the vehicle-treated group (13.3 mg) ($p < 0.05$). An increase in the production of MPO activity was recorded after topical administration of TPA (385.4 unit of MPO/site) and the group receiving the EEST was able to decrease its activity (258.1 unit of MPO/site) ($p < 0.05$), indicating a reduction of neutrophil migration. All data are shown in Figure 4.

Different essay investigating the anti-inflammatory activity of *S. terebinthifolius* leaves and stem bark resulted in reduction of leucocyte accumulation and of pro-inflammatory cytokine and decrease of edema, demonstrating a remarkable potential of this pepper in the improvement of inflammation (Estevão et al., 2017; Nunes-Neto et al., 2017; Silva et al., 2017).

Few studies have investigated the anti-inflammatory activity of *S. terebinthifolius* fruits. An *in vitro* assay made with fruit peels suggest that the flavonoids present in the pepper are responsible for the inhibition of NO production by macrophages and an *in vivo* experiment with the fruits essential oil resulted in a marked anti-inflammatory activity (Bernardes et al., 2014; Formagio et al., 2011).

Myeloperoxidase expressed by innate immune cells, such as neutrophils and monocytes, can be used as diagnostic of inflammatory diseases (Lamprecht et al., 2018), and the EEST was able to decrease the innate immune cells migration, exhibiting an anti-inflammatory capacity.

Transcription factors involved in inflammatory diseases can be activated by free radical species, being interesting to investigate them. A study evaluated the anti-inflammatory activity induced by carrageenan of *S. terebinthifolius* leaves and isolated compound methyl gallate, and found that the oral treatment with methanolic extract did not alter MPO activity, neither the oral or intraplantar administration of methyl gallate, but they inhibited the edema formation (Silva et al., 2017).

The antioxidant activity of EEST *in vivo* is shown in Figure 5. The administration of TPA altered the redox state of the tissue (0.41 µM of ferrous sulphate) detected by the FRAP assay when compared to the ears treated with acetone (0.77 µM of ferrous sulphate) ($p < 0.05$), but the EEST did not inhibited these changes (0.46 and 0.42 µM of ferrous sulphate). As expected, TPA administration significantly decreased the catalase activity (37.3 U/mg of protein) ($p < 0.05$), however the EEST was not able to reverse the antioxidant enzyme depletion (35.3 and 35.1 U/mg of protein). Change in SOD activity was not observed between groups.

Most of the studies that evaluated the antioxidant activity of *S. terebinthifolius* fruits were carried out *in vitro*, and show that both essential oil and different extracts have antioxidant activity probably related to the content of secondary metabolites present in this species

(Bendaoud et al., 2010; Bernardes et al., 2014; Costa et al., 2015; Ennigrou et al., 2016; Salem et al., 2018; Tlili et al., 2018).

A study carried out in cell culture showed that the methanolic extract of *S. terebinthifolius* leaves possesses beneficial properties reducing doxorubicin-induced oxidative stress in human erythrocytes, probably via antioxidant effects by inhibiting free radicals and increasing antioxidant enzyme activity (SOD and GPx) (Rocha et al., 2017).

In addition, in an animal model trial, the *S. terebinthifolius* stem bark was evaluated for its neuroprotective effects in a rotenone model of Parkinson's disease and the ethanolic extract inhibited lipid peroxidation, suggesting a neuroprotective effect mediated by its antioxidant activity (Sereniki et al., 2016).

An animal model study that investigated the protective effect of *Pistacia lentiscus* oil, species from the same botanical family of *S. terebinthifolius*, in the oxidative stress involved in bleomycin-induced lung fibrosis, found that the oil pretreatment reversed all bleomycin-induced oxidative stress parameters disturbances, such as lipoperoxidation and antioxidant enzymes (SOD and CAT) depletion (Abidi et al., 2017). Nevertheless, in current research, EEST did not reverse the antioxidant enzymes depletion, although it presented antioxidant activity *in vitro*.

4 CONCLUSIONS

The results confirm the antiradicalar activity of the AEST and EEST fruits by the DPPH method previously described in the literature and contribute to elucidate the other antioxidant mechanisms that include the antiradicalar activity represented by the ABTS and NO radicals, the reduction of ferric ion and the oxidation inhibition involving oxidizable substrates, such as lipids. This antioxidant activity may be associated with the content of gallic and caffeic acids

and the flavonoids naringenin and quercetin. And unlike some plant extracts, extracts of *S. terebinthifolius* do not present metal chelating activity.

In relation to the EOST, γ-3-carene, α-felandren, β-felandren, α-pinene and elemol represent the major compounds found and results of antioxidant activity were observed by inhibition of DPPH and ABTS radicals and by reduction of ferric ion.

The EEST fruits was able to reduce ear edema induced by TPA by anti-inflammatory mechanism such as the decrease of MPO activity, but not by antioxidants mechanisms such as reduction potential or increased activity of enzymes (CAT and SOD).

ACKNOWLEDGEMENTS

This study was financed in part by the Conselho Conselho Nacional de Desenvolvimento Científico e Tecnológico – Brasil (CNPq), the Fundação de Apoio à Pesquisa e a Inovação Tecnológica do Estado de Sergipe (Fapitec/SE) - Brasil, the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES - Finance Code 001), and the Financiadora de Estudos e Projetos - Brasil (FINEP). And is part of N. B. Macedo's Master Thesis, which was present to Post-Graduate Program in Nutrition Sciences (PPGCNUT), Federal University of Sergipe, Brazil.

CONFLICT OF INTEREST

The authors declare no competing financial or personal interest.

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Table 1 – Yield and content of phenolic compounds and total flavonoids of the aqueous and ethanolic extracts of *S. terebinthifolius*.

Extract	Yield (%)	Total Phenolic (mg in gallic acid equivalent / g extract)	Total Flavonoids (mg in catechin equivalent / g extract)
AEST	20.98	16.22 ± 0.73	0.40 ± 0.29
EEST	30.23	17.48 ± 0.11	15.12 ± 5.61

AEST: Aqueous extract of *S. terebinthifolius*. EEST: Ethanolic extract of *S. terebinthifolius*.

Table 2 – Content (μg/mg) of compounds in aqueous and ethanolic extracts of *S. terebinthifolius* fruits.

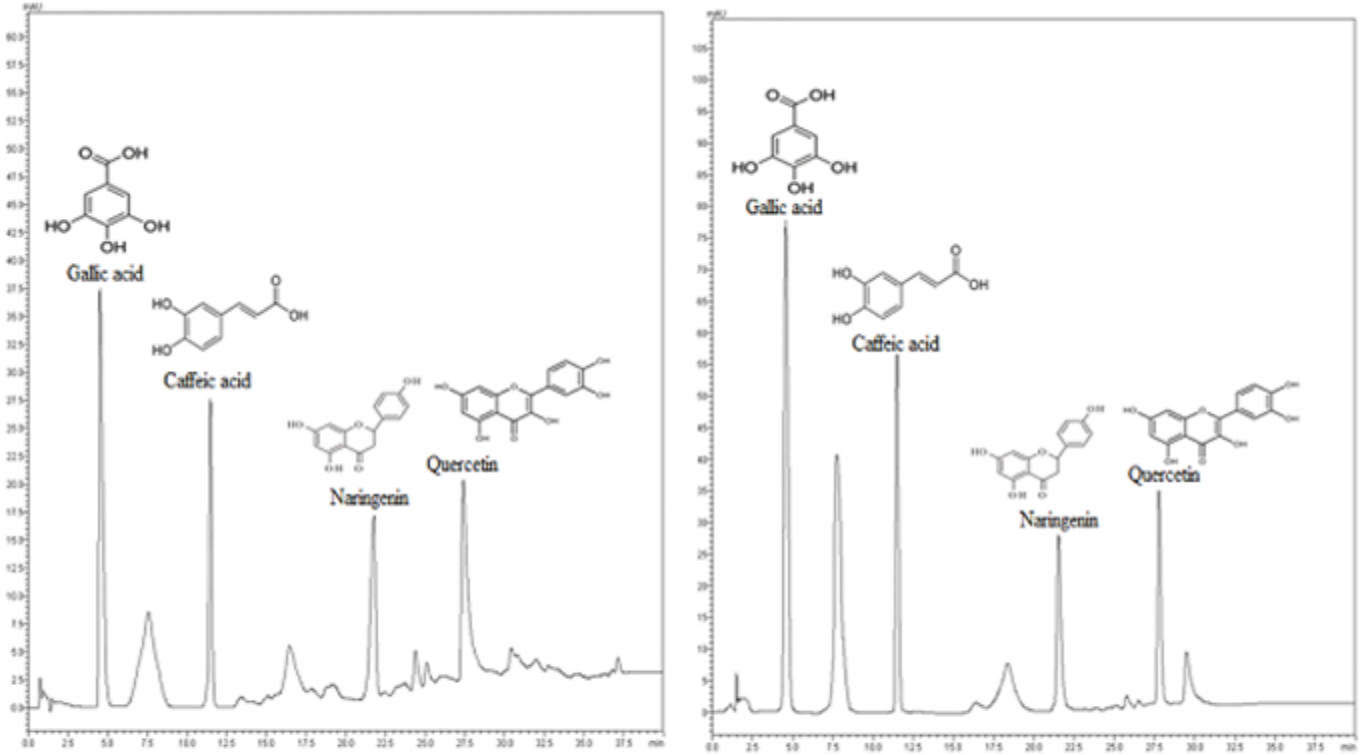
Compounds	AEST (Mean ± SD)	EEST (Mean ± SD)
Gallic acid	21.66 ± 0.12	50.96 ± 0.11
Caffeic acid	13.08 ± 0.09	30.50 ± 0.38
Naringenin	8.55 ± 0.15	19.88 ± 0.19
Quercetin	11.13 ± 0.11	22.07 ± 0.25

AEST: Aqueous extract of *S. terebinthifolius*. EEST: Ethanolic extract of *S. terebinthifolius*. SD: Standard deviation.

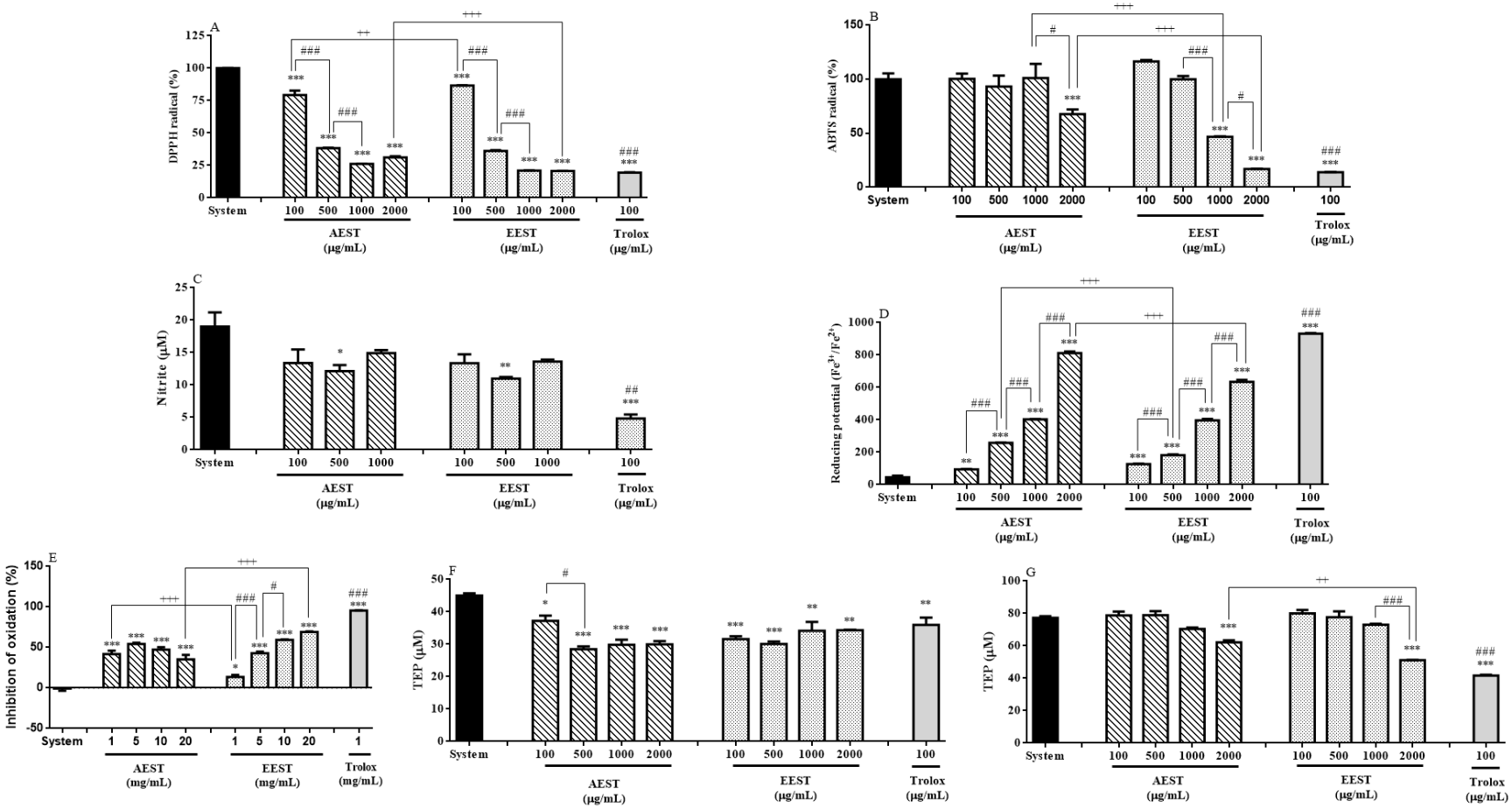
Table 3 – Chemical composition of the essential oil obtained by hydrodistillation from *S. terebinthifolius* fruits.

Peak	Compound	RT	CG/EM/FID (%)
1	α-pinene	8.559	13.60
2	β-pinene	9.880	0.27
3	Myrene	10.220	2.21
4	α-felandren	10.726	22.80
5	γ-3-carene	10.931	33.03
6	p-cymene	11.358	0.63
7	β-felandren	11.518	12.65
8	γ-elemeno	21.189	0.49
9	(E)-caryophyllene	23.646	1.88
10	Germacrene D	25.310	2.56
11	Elemol	27.009	7.44
12	γ-eudesmol	29.180	0.89
13	β-eudesmol	29.703	1.57
			100.00

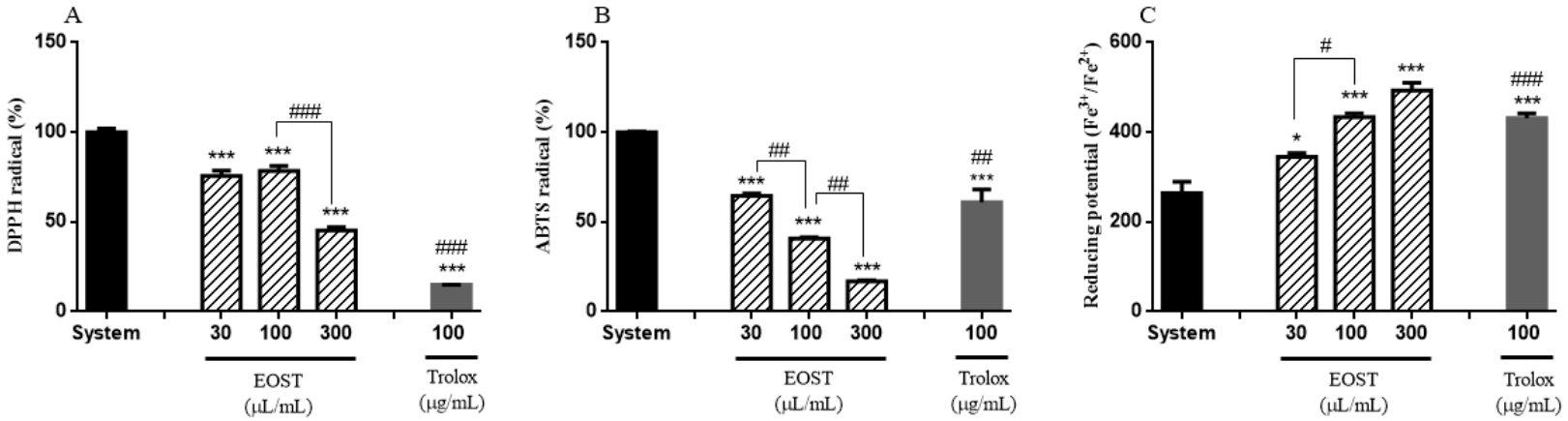
RT: retention time in minutes; GC/MS/FID: gas chromatography / mass spectrometry / flame ionization detector.



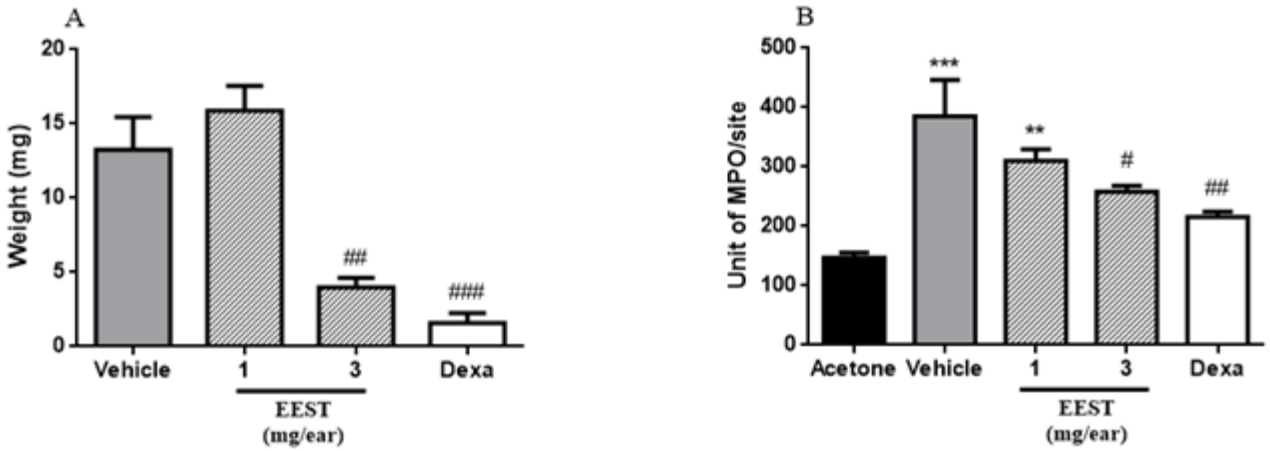
MACEDO, N.B. Figure 1 – HPLC chromatograms of aqueous and ethanolic extracts, respectively, of *S. terebinthifolius* fruits (λ = 280 nm). Gallic acid (RT: 4.7 min), caffeic acid (RT: 11.5 min), naringenin (RT: 21.8 min) and quercetin (RT: 27.7 min).



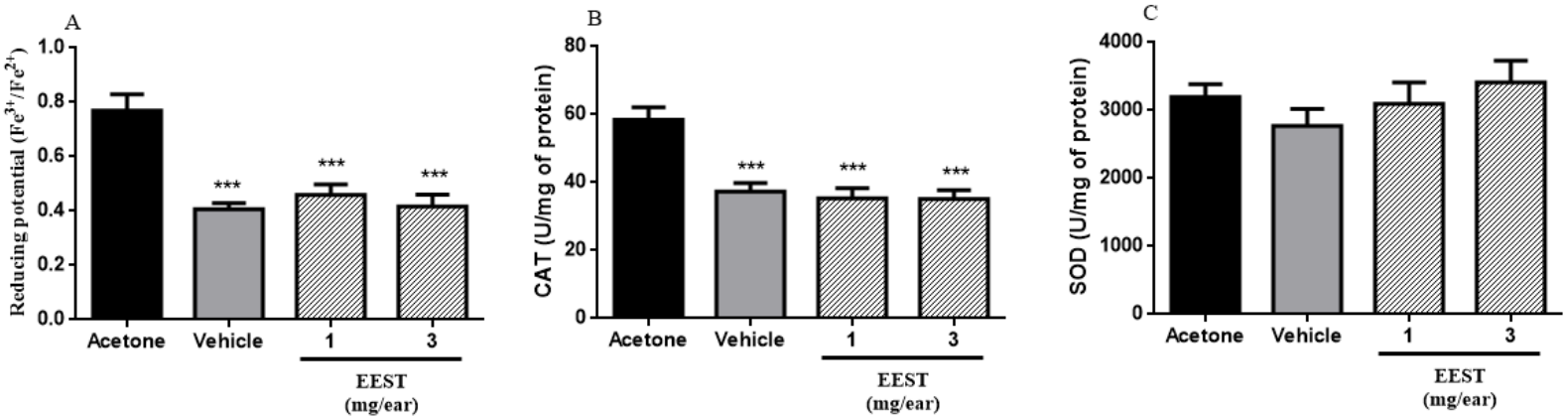
MACEDO, N.B. Figure 2 – Antioxidant activity of aqueous (AEST) and ethanolic extracts (EEST) of *S. terebinthifolius in vitro*. AEST and EEST were tested in the DPPH radical assay (A), ABTS radical assay (B), nitric oxide scavenging activity (C), ferric reducing/antioxidant power (FRAP) (D), co-oxidation of β-carotene/linoleic acid (E), inhibition of spontaneous (F) and induced by ferric chloride (G) lipid oxidation. The results express the mean ± SEM of the values. * p <0.05 and ** p <0.01 and *** p <0.001 vs system (reaction medium without antioxidant); # p <0.05 and ## p <0.01 and ### p <0.001 between concentrations and between the concentration of 100 µg/mL or 1 mg/mL of the extracts vs Trolox; ++ p <0.01 and +++ p <0.001 between concentrations of different extracts; (One-way ANOVA followed by Tukey's test).



MACEDO, N.B. Figure 3 – Antioxidant activity of essential oil of *S. terebinthifolius* (EOST) *in vitro*. EOST was tested in the DPPH radical assay (A), ABTS radical assay (B) and ferric reducing/antioxidant power (FRAP) (C). The results express the mean ± SEM of the values. * $p < 0.05$ and *** $p < 0.001$ *vs* system (reaction medium without the antioxidant); # $p < 0.05$ and ## $p < 0.01$ and ### $p < 0.001$ between concentrations and between the concentration of 100 µg/mL of essential oil *vs*. Trolox; (One-way ANOVA followed by Tukey's test).



MACEDO, N.B. Figure 4 - Anti-inflammatory effect of ethanolic extract of *S. terebinthifolius* (EEST) administration on TPA-induced ear edema. Mice were submitted to ear inflammation caused by TPA, concomitant with treatment with the EESTs (1 or 3mg/ear) or dexamethasone (Dexa). The weight of the ears (A) and MPO activity (B) were measured 6 h thereafter in ears. #p < 0.5 or ##p < 0.01 or ###p < 0.001 vs. vehicle-treated group; **p < 0.01 or ***p < 0.001 vs. acetone-treated group (One-way ANOVA followed by Tukey's test).



MACEDO, N.B. Figure 5 - Antioxidant effect of ethanolic extract of *S. terebinthifolius* (EEST) administration on TPA-induced ear edema. Mice were submitted to ear inflammation caused by TPA, concomitant with treatment with the EESTs (1 or 3mg/ear). The redox state (FRAP) (A), catalase (B) and SOD (C) enzymes concentrations were measured 6 h thereafter in ears. ***$p < 0.001$ vs. acetone-treated group (One-way ANOVA followed by Tukey's test).

5 CONCLUSÕES

Na revisão da literatura, foram identificados como componentes principais o grupo dos compostos fenólicos para os extratos e o grupo dos terpenos para o óleo essencial, variando o teor de acordo com as diferentes partes da *S. terebinthifolius* e foram descritas como atividades biológicas principais a atividade antimicrobiana, cicatrizante, anti-inflamatória e antioxidante. No entanto, estas duas últimas atividades apresentam resultados inconclusivos e pouco explorados no fruto, o que justificou os demais objetivos deste trabalho. Desta forma, os resultados obtidos na avaliação da capacidade antioxidante indicam boa atividade de captura de radicais livres em ambos extratos, sendo que o extrato etanólico mostrou melhor atividade de captura do radical ABTS. Foi observada boa atividade redutora, principalmente do extrato aquoso, e proteção contra oxidação lipídica de ambos extratos. Esta atividade pode estar associada ao conteúdo dos ácidos gálico e cafeico e dos flavonoides naringenina e quercetina. Já no óleo essencial os compostos γ-3-careno, α-felandreno, β-felandreno, α-pineno e elemol representam mais de 80% dos compostos encontrados e foi observada atividade antioxidante pela captura de radicais livres e pelo potencial de redução. Além disso, foi visto que o extrato etanólico diminuiu o edema de orelha via mecanismo anti-inflamatório de redução da atividade da mieloperoxidase. Desse modo, a avaliação dos compostos presentes no fruto de *S. terebinthifolius* indicam que esta pimenta pode representar uma fonte de compostos com importante atividade biológica e assim, deve ser melhor explorada e compreendida, reforçando o papel que as ervas e especiarias tem na culinária e seus possíveis benefícios à saúde.

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ANEXO A – PARECER DO COMITÊ DE ÉTICA

UNIVERSIDADE FEDERAL DE SERGIPE
PRÓ-REITORIA DE PÓS-GRADUAÇÃO E PESQUISA
COORDENAÇÃO DE PESQUISA
COMITÊ DE ÉTICA EM PESQUISA COM ANIMAIS (CEPA)

UFS

CERTIFICADO

Certificamos que a proposta intitulada "**Pimenta rosa (Schinus terebinthifolius Raddi):atividade antioxidante, anti-inflamatória e possível efeito na diferenciação de adipócitos**", registrada com o **nº 48/2017**, sob a responsabilidade da **Profª. Drª. Ana Mara de Oliveira e Silva** que envolve a produção, manutenção ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e foi aprovada pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) da Universidade Federal de Sergipe, em reunião de **15/01/2018**.

Finalidade	( ) Ensino (X) Pesquisa Científica
Vigência da autorização	Início:09/02/2018, Término: 03/06/2018
Espécie/linhagem/raça	Camundongo Heterogênico/Swiss/
Nº de animais	63
Peso/Idade	25-30g / 60 dias
Sexo	M
Origem	Biotério Setorial do Departamento de Fisiologia da UFS.

Josemar Sena Batista

Prof. Dr. JOSEMAR SENA BATISTA
Coordenador do CEPA/UFS

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